Overview Information

Agency Name: Department of Health and Human Services, Office of the Secretary, Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority 330 Independence Avenue, SW, Rm G640, Washington, DC, 20201

Issuing Office: Department of Health and Human Services, Office of the Secretary, Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority (BARDA) 330 Independence Avenue, SW, Rm G640, Washington, DC, 20201

Research Opportunity Title: BARDA Broad Agency Announcement for the Advanced Research and Development of Chemical, Biological, Radiological, and Nuclear Medical Countermeasures

Announcement Type and Date: Initial Announcement, March 4, 2009

Eligible Applicants: This BAA is open to **ALL** responsible sources. Offerors may include single entities or teams from private sector organizations, Government laboratories, Federally Funded Research and Development Centers (FFRDCs), and academic institutions.

Federally Funded Research and Development Centers (FFRDCs), are eligible to respond to this BAA, individually or as a team member of an eligible principal Offeror, as so long as they are permitted under the sponsoring agreement between the Government and the specific FFRDC.

To be eligible for award, a prospective recipient must meet certain minimum standards pertaining to financial resources, ability to comply with the performance schedule, prior record of performance, integrity, organization, experience, operational controls, technical controls, technical skills, facilities, and equipment.

Historically Black Colleges and Universities (HBCU), Minority Institutions (MI), Small Business concerns, Small Disadvantaged Business concerns, Women-Owned Small Business concerns, Veteran-Owned Small Business concerns, Service-Disabled Veteran-Owned Small Business concerns, and HUB Zone Small Business concerns are encouraged to submit proposals and to join other entities as team members in submitting proposals. However, no portion of this BAA will be set-aside pursuant to FAR Part 19.502-2.

Research Opportunity Description: The Biomedical Advanced Research and Development Authority solicits the advanced research and development of medical countermeasures for chemical, biological, radiological, and nuclear agents that threaten the U.S. civilian population. BARDA anticipates that research and development activities awarded under this BAA will serve to advance candidate medical countermeasures towards FDA licensure/approval and consideration for acquisition.

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INTRODUCTION

This Broad Agency Announcement (BAA), which sets forth research areas of interest for the Biomedical Advanced Research and Development Authority (BARDA), is issued under paragraph 6.102(d)(2) of the Federal Acquisition Regulation (FAR). Proposals selected for award are considered to be the result of full and open competition and in full compliance with the provision of Public Law 98-369, "The Competition in Contracting Act of 1984" and subsequent amendments.

BARDA, the lead agency for acquisition of medical countermeasures (MCM) within the Office of the Assistant Secretary for Preparedness and Response (ASPR), U.S. Department of Health and Human Services (HHS) is soliciting proposals for the advanced research and development of MCM for chemical, biological, radiological, and nuclear (CBRN) agents that threaten the U.S. civilian population. The continuing threat of terrorism underscores the compelling need to develop new and improved MCM for protecting all segments of the civilian population. This BAA will support the development of candidate products and diagnostic tools to meet the challenging lifecycle requirements of CBRN MCM (e.g. post-exposure efficacy, extended shelf life, storage, distribution, and dispensing).

BARDA's priorities are aligned with the preparedness mission of the HHS Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), as articulated in the PHEMCE Implementation Plan (http://www.hhs.gov/aspr/barda/phemce/index.html). To that end, BARDA supports the advanced research/development and acquisition of MCM such as vaccines, therapeutics, and diagnostics.

The Pandemic and All Hazard Preparedness Act (PAHPA; http://www.hhs.gov/aspr/opsp/pahpa/index.html) directs BARDA to promote (i) innovations in technologies that may assist MCM advanced research and development, (ii) research and development of tools, devices, and technologies, and (iii) research to promote strategic initiatives, such as rapid diagnostics, broad spectrum antimicrobials, and vaccine manufacturing technologies.

The BAA is open to all responsible sources. Offerors may include single entities or teams from private sector organizations, Government laboratories, Federally Funded Research and Development Centers (FFRDCs), and academic institutions.

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encouraged to submit proposals and to join other entities as team members in submitting proposals. However, no portion of this BAA will be set-aside pursuant to FAR Part 19.502-2.

The purpose of this BAA is to solicit proposals that focus on one or more of the following solicited areas of interest as listed here and further described in Part I of this announcement.

Research Areas of Interest:

- Vaccines
- Antitoxins and Therapeutics
- Antimicrobial Drugs
- Radiological and Nuclear Threat Countermeasures
- Chemical Threat Countermeasures
- Clinical Diagnostic Tools

Research and technical objectives are described in Part II and efforts proposed by Offerors may include activities in Non-Clinical Research and Development, Process Development, Formulation, and Manufacturing Development, and Clinical Evaluation. For drug and biologic medical countermeasure development efforts, Offerors shall propose a Statement Of Work (SOW) consistent with activities between Integrated Technology Readiness Levels (TRLs) 6 to 7 (see Attachment 1). For Clinical Diagnostic Tools, Offerors shall propose a SOW consistent with activities between TRLs 5 to 6 (see Attachment 2).

The BAA will be conducted in two stages:

In Stage 1, Offerors shall submit a Quad Chart and White Paper summarizing the proposed project. All Quad Charts and White Papers must be prepared in accordance with the instructions contained in Part IV, and may be submitted at any time during the BAA. Brochures or other descriptions of general organizational or individual capabilities will not be accepted. Acknowledgement of receipt (electronic) will be made within one week. Decision letters to Offerors will be sent within 90 days of submission.

In Stage 2, Offerors receiving a favorable evaluation will be asked to prepare a Full Proposal and submit to BARDA within 90 days. Instructions for completing the Full Proposal are found in Part IV of this announcement. A request to submit a Full Proposal does not assure an award. There are no specified funding limitations identified for proposals submitted under this BAA. The budget shall be commensurate with the nature and complexity of the proposed research. The Government intends to make an award decision within 180 days after submission of Full Proposals.

Offerors contemplating submitting Quad Charts, White Papers, and Full Proposals are strongly encouraged to contact the appropriate technical Point of Contact (POC) at BARDA (see names and e-mail addresses listed immediately after each research area of interest). Offerors are advised that only a Contracting Officer may obligate the Government to any agreement involving expenditure of Government funds.

The costs of preparing responses to this BAA are not considered an allowable direct charge on any resultant award.

Quad Chart and White Papers and / or Full Proposals WILL NOT BE ACCEPTED after 4:30 PM (Eastern Standard Time) on 12/31/2009.

In accordance with federal statutes, regulations, and HHS policies, no person on grounds of race, color, age, sex, national origin, or disability shall be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity receiving financial assistance from the HHS.

BARDA reserves the right to fund all, some, or none of the proposals submitted; may elect to fund only part of a submitted proposal; and may incrementally fund any or all awards under this BAA. While award is anticipated to occur according to the stated schedule, BARDA may select for funding any Full Proposal or portions of a proposal at any time. Offerors that are not responsive to BARDA requests for information in a timely manner, defined as meeting government deadlines established and communicated with the request, may be removed from award consideration.

BARDA reserves the right to award the instrument best suited to the nature of the research proposed and may award any appropriate contract type under the Federal Acquisition Regulation. BARDA may, in the future, also elect to make awards in the form of grants, cooperative agreements, or other transactions (OT) agreements resulting from this BAA as appropriate.

Multiple awards of various values are anticipated and are dependent upon the proposals' scientific and technical merits, how well the proposals fit BARDA's areas of interest and available funding.

Anticipated funding for the program (not per contract or award) may range from $25M to $750M dollars subject to congressional approval. This funding profile is an estimate only and will not be a contractual obligation for funding. All funding is subject to change due to government discretion and availability.

All administrative inquires regarding this BAA shall be addressed to CBRN-BAA@hhs.gov. Technical questions shall be referred to the Point Of Contacts (POCs) shown following each research area of interest. When an inquiry is made, please include all pertinent contact information.

This BAA is available on the following websites:

https://www.fbo.gov
https://www.medicalcountermeasures.gov/
http://www.hhs.gov/aspr/barda/

This BAA is a continuously open announcement valid throughout the period from the date of issuance through 31 December 2009, unless announced otherwise. Amendments to this BAA will be posted to the websites listed above when they occur. Interested parties are encouraged to periodically check these websites for updates and amendments.

MICHAEL A. BALADY, Ph.D.
HEAD OF CONTRACTING ACTIVITY
HHS/OS/ASPR/BARDA

Pre-Proposal Conferences:

Note: Offerors are encouraged to attend one or both of the conferences. However, the March 24th conference will have limited seating.

Pre-proposal #1. March 10, 2009 from 1-3 pm for research area 1: vaccines, research area 2: antitoxins and therapeutics.

200 Independence Avenue S.W.
Hubert H Humphrey Building 8th floor Room 800
Washington, DC 20201

Please note the following regarding the pre-proposal conference:
1. Enter the Humphrey Building at the Independence Avenue Street entrance.
2. Arrive 30 minutes early to allow time to clear security.
3. Bring your identification
4. The closest metro stop is Federal Center SW
5. Attendance is limited to a maximum of two (2) people per company. Email the names of your attendees to glynis.fisher@hhs.gov by March 6, 2009.
6. Tape recorders and videos are prohibited.
7. Minutes of the conference will be posted on FedBizOpps in an amendment to the BAA approximately 1 week after the pre-proposal conference

Pre-proposal #2. March 24, 2009 from 1-3 pm for research area 3: antimicrobial drugs; research area 4: radiological/nuclear threat medical countermeasures; research area 5: chemical threat medical countermeasures and research area 6: clinical diagnostics tool.

330 Independence Ave. S.W.
Switzer Building 3rd floor room 3005
Washington, DC 20201

Please note the following regarding the pre-proposal conference:
1. Enter the Switzer Building at the C Street entrance.
2. Arrive 30 minutes early to allow time to clear security.
3. Bring your identification
4. The closest metro stop is Federal Center SW
5. Attendance is limited to a maximum of two (2) people per company. Email the names of your attendees to glynis.fisher@hhs.gov by March 18, 2009.
6. Tape recorders and videos are prohibited.
7. Minutes of the conference will be posted on FedBizOpps in an amendment to the BAA approximately 1 week after the pre-proposal conference

NOTE: For those who are unable to attend, please use the following dial-in information: 1-866-917-6472 Participant code # 7938647.

Part I: Research Areas of Interest

Through this solicitation, BARDA seeks to support advanced research and development strategies in the following research areas of interest. Offeror shall review Part II: Research and Technical Objectives. This section presents the CBRN-related technical objectives that BARDA seeks to achieve through this BAA.

Area of Interest #1: Vaccines

1.1 Development of new vaccine/adjuvant formulations; use of approved or novel adjuvants in conjunction with a specific vaccine to achieve desired improvements like enhanced efficacy, antigen-sparing or lower adverse effects.

1.2 Development of broad-base platform technologies that may be used in vaccine development for multiple antigens/agents.

1.3 Development of desired capability improvements for vaccine attributes such as enhancements in formulation and delivery methods, time to protection, duration of protection, product stability and shelf-life.

1.4 Product development of a vaccine/adjuvant candidate formulated for a specific application including non-clinical, clinical development, manufacture at pilot scale under GMP; process development and scale up including fill-finish; assay methods for drug substance and product release, stability, and characterization.

Note: Special Instructions apply to the review cycle for this research area of interest. Please refer to Part VI for additional information.

Technical Point of Contact: Dr. Narayan Iyer; narayan.iyer@hhs.gov

Area of Interest #2: Antitoxins and Therapeutics

2.1 Screening of small molecule libraries for broad activities against botulinum toxins, anthrax toxins, and filoviruses, and subsequent development and characterization of promising lead compounds.

2.2 Development of a multivalent botulinum toxoid for vaccine and hyper-immune plasma production.

2.3 Development of peptide or small molecule antitoxins, and other novel compounds, with innovative formulations offering enhanced long-term stability.

2.4 Development of monoclonal anthrax antitoxins including non-clinical, completion of a phase 1 trial; development of a phase 2 clinical development, manufacture at pilot scale under GMP; process development and scale up including fill-finish.

2.5 Development of an intramuscular formulation of monoclonal anthrax antitoxins.

2.6 Development of monoclonal antibody treatments and other therapeutics for agents of viral hemorrhagic fevers.

Note: Special Instructions apply to the review cycle for this research area of interest. Please refer to Part VI for additional information.

Technical Point of Contact: Dr. Stephen Morris; stephen.morris@hhs.gov

Area of Interest #3: Antimicrobial Drugs

3.1 Screening of small molecule libraries for activities against bacterial biodefense pathogens orthopox viruses, agents of viral hemorrhagic fevers, and other biodefense threat agents, and subsequent development of promising lead compounds.

3.2 Development of novel peptide or small molecule antiviral candidates or development of current peptides or small molecules with innovative formulations offering enhanced long-term stability.

3.3 Repurposing or combining of currently licensed antibiotics for prophylactic or therapeutic use against one or more biodefense threat agents.

Technical Point of Contact: Dr. Dawn Myscofski; dawn.myscofski@hhs.gov

Area of Interest #4: Radiological/Nuclear Threat Medical Countermeasures

4.1 Development of mitigators or treatments for subsyndromes associated with Acute Radiation Syndrome (ARS) and the Delayed Effects of Acute Radiation Exposure (DEARE), arising from exposure to ionizing radiation. Treatments that have efficacy when administered no earlier than 24 hours post irradiation are of particular interest. Subsyndromes of interest include:

Neutropenia
Thrombocytopenia
Gastrointestinal
Skin (Cutaneous)
Lung (Pulmonary)
Kidney (Renal)
Brain (central nervous system)

4.2 Development of Decorporation agents (isotopes of interest: Co-60, Cs-137, U-235/238, Pu-238/239, Sr-90, Am-241, Po-210, other transuranics) or new formulations of existing countermeasures (e.g., improved ease of administration).

4.3 Development of a biodosimetry self assessment tool for exposures to ionizing radiation at or greater than 2 Gy.

4.4 Development of a rapid point-of-care diagnostic or centralized high-throughput for assessing absorbed doses of ionizing radiation in the range of 0.5 Gy to 10 Gy that has a viable assessment signal at least 24 hours after exposure that persists up to one month after exposure.

4.5 Development of an improvement on the current "gold standard" for assessing absorbed doses of ionizing radiation (the dicentric chromosomal assays (DCA)) in terms of ease of use, time for performance, statistical certainty of dose, improved signal, and biomarker lifespan.

Note: Special Instructions apply to the review cycle for this research area of interest. Please refer to Part VI for additional information.

Technical Point of Contact: Dr. Ronald G. Manning; ronald.manning@hhs.gov

Area of Interest #5: Chemical Threat Medical Countermeasures:

5.1 Nerve Agents:

5.1.1 Development of medical countermeasures (MCM) such as an improved anticonvulsant to replace or supplement diazepam, (faster acting after intramuscular administration; better efficacy, particularly after seizures are established; better efficacy in children).

5.1.2 Development of a neuroprotectant to prevent and treat hypoxic and/or excitotoxic brain damage.

5.1.3 Development of an improved acetylcholinesterase reactivator to replace pralidoxime chloride (e.g., broad spectrum; centrally acting)

5.1.4 Development of an improved anticholinergic to supplement atropine (longer acting and centrally acting).

5.1.5 Development of new formulations of existing antidotes (more easily administered; faster acting).

5.1.6 Development of easily administered and rapidly effective countermeasures that can be used by untrained persons and by first responders dealing with large numbers of exposed individuals. Ease of administration in mass casualty situations should take into account the practical limits of injected medications versus inhaled, intranasal and sublingual administration. These alternative routes may fail if persons have profuse respiratory secretions. Autoinjector intramuscular injection may continue to be a preferred route of administration for many compounds under most circumstances.

5.1.7 Development of chemical decontamination solutions for use on intact /or injured human skin (improved efficacy compared to soap and water).

5.1.8 Development of medical diagnostic tools that are sensitive, specific, rapid and easily transferable to hospitals and clinical laboratories.

5.2 Pulmonary Agents: Development of anti-inflammatory drugs and other medical countermeasures to treat and prevent lung damage from exposure to agents such as chlorine and phosgene.

5.3 Vesicants: Development of medical countermeasures that limit harmful aspects of the inflammatory response following exposure to vesicating agents such as mustards and Lewisite, including topical (skin and eye) and systemic preparations.

5.4 Blood/Metabolic Agents: Development of medical countermeasures to treat poisoning from agents such as cyanides and fluoroacetates under those circumstances where response personnel are immediately present during the limited time between exposure and fatal outcome.

5.5 Toxic Industrial Chemicals and Emerging Threats: Development of medical countermeasures that protect from a wide range of unconventional threats in response to new population threat assessments.

Note: Special Instructions apply to the review cycle for this research area of interest. Please refer to Part VI for additional information.

Technical Point of Contact: Dr. Ronald G. Manning; ronald.manning@hhs.gov

Area of Interest #6: Clinical Diagnostics Tools:

6.1 Development and evaluation of rapid *in vitro* diagnostic devices, using available or emerging technological platforms to detect or differentiate specific bio-threat pathogens or toxins in a variety of relevant clinical matrices. The assay system should enable early differential diagnosis of disease with high predictive value. Automated systems should incorporate automated, integrated sample preparation/processing and results-analysis software for ease of use by non-expert personnel at point-of-care. Design and production of the system must be compliant with U.S. Quality Systems Regulations (21 CFR Part 820).

6.2 Development and evaluation of new analytical methods to quantitate circulating toxin levels.

6.3 Development and production of characterized, stable diagnostic reagents for assay systems. Reagents should ideally be room-temperature stable with greater than two years shelf life and non-IP burdened.

6.4 Development and clinical evaluation of simple, reliable sample collection and sample preparation methods/systems.

Technical Point of Contact: Ms. Donna Boston; donna.boston@hhs.gov

Part II: Research and Technical Objectives

The topics listed below exemplify some of the typical developmental activities in the areas of non-clinical research, manufacturing, clinical evaluation, project management, and regulatory strategy contained in a typical drug, biologic or device development effort. This information is provided to assist and guide Offerors in preparing their Statement of Work (SOW). Offerors shall submit a SOW in their proposal that addresses these topics as appropriate. Provide as much detail as may be necessary to fully explain the proposed technical approach or method.

For drug and biologic medical countermeasure development efforts, Offerors shall propose a SOW that is consistent with activities occurring during Integrated TRLs 6 to 7 (see Attachment 1). For diagnostics, Offerors shall propose a SOW that is consistent with activities occurring during TRL 5 to 6 (see Attachment 2).

Proposal preparation and submission instructions are contained in Part IV along with special instructions contained in Part VI.

A. Development Approach:

1. Non-Clinical Research and Development Representative Activities include but are not limited to:

a. Screening of small molecule libraries for antitoxin/antimicrobial/antiviral activities (for already approved or licensed product).
b. Evaluating the safety, immunogenicity, efficacy, pharmacokinetics / pharmacodynamics, bioavailability, solubility, formulation, dose, route and schedule of the medical countermeasure using both in vitro and animal models following Good Laboratory Practice guidelines (GLP: as defined in the U.S. Code of Federal Regulations -21CFR Part §58), as and when appropriate.
c. Development of analytical methods and assays appropriate for product characterization and product release, including tests for the identity, purity, potency, and stability of the bulk drug substance and final drug product. Offerors shall identify a stable source and availability of reagents and reference standards for these assays required.
d. Development of Validation Protocol for analytical and assay methods to defining product manufacturing control, performance, potency and product stability indication.

2. Process Development, Formulation, and Manufacturing Development Representative Activities include but are not limited to:

a. Development of master and working cell banks under Good Manufacturing Practice guidelines (GMP: as defined in the U.S. Code of Federal Regulations – 21 CFR §211).
b. Process development activities to increase efficiency, yield, quality, and reduce the variability and risk factors in the manufacture of the drug substance and drug product.

c. Formulation development to evaluate combinations of excipients and their influence on the target product profile and stability.
e. Manufacture of non-GMP and of GMP pilot lots of candidate product in amounts sufficient to carry out required/proposed non-clinical and Phase 1 and/or Phase 2 clinical trials.
f. Identification of Critical Quality Attributes (CQA) and Critical Process Parameters.
g. Manufacturing scale-up plan to lead to consistency lot manufacturing of the candidate product.
h. Process flow for personnel, material and waste disposal.
i. Proposed packaging design and execution of fill-finish of final drug product.
j. Design of stability testing plan and conduct of stability studies on bulk and final product.
k. Develop a Risk Evaluation and Mitigation Strategy or similar risk mitigation strategy proposal

3. Clinical Evaluation Representative Activities include but are not limited to:

a. Design and conduct of Phase 1 clinical trials to evaluate the safety and pharmacokinetics of the therapeutic candidate/product in humans in accordance with Good Clinical Practice guidelines (GCP: as defined by 21 CFR §312 and ICH Guidelines document E6.
b. Design and conduct of a Phase 2 clinical trial in accordance with all Federal regulations and GCP guidelines.

B. Management Approach:

1. Integrated Product Development Plan (IPDP) Representative Activities include but are not limited to:

a. Activities and stages of product development that the Offeror is proposing to perform under contract funding in a project plan that indicates the base period and option period activities and includes all of the functional areas of development listed below.
b. A detailed description of the experimental design, including the rationale for experimental approaches, and a description of alternative approaches to be employed if these methods do not achieve the defined goals.
c. Distinct stages of the product development pathway that are gates for Go/No Go decisions for advancing to the next stage of the Integrated Product Development Plan.
d. The qualitative and quantitative criteria and accompanying data used to assess the scientific merit and technical feasibility of proceeding to the next stage of product development.
e. Milestones and timelines for the initiation, conduct, and completion of product development activities for each stage with a budget (in direct costs) linked to each stage.

f. A listing of key personnel (including proposed consultants) who possess the necessary education, training, and experience to successfully perform the work identified in the technical proposal and their resumes
g. A staffing plan that indicates personnel (in house and contracted) resources and the percentage of time to be dedicated to perform the work.
h. A clear and comprehensive regulatory master plan that focuses on the crucial pathway integrating all products, risk evaluation and mitigation at all development stages, non-clinical and clinical testing, and manufacturing activities using the most current and available information, including documented and time-relevant consultation with FDA.
i. Establishment and filing of regulatory submissions to the relevant FDA center.
j. A plan for additional studies to support future filing for FDA-approval/clearance.
k. Summary of any prior communication with the FDA relevant to the product development; summary of audits and inspections.
l. Tentative schedule of regulatory milestones.
m. Potential Plan for consideration of an Emergency Use Authorization (EUA) of a medical product (http://www.fda.gov/oc/guidance/emergencyuse.html)
n. A work breakdown structure (WBS) that is discernable and consistent. It may include data at the cost account level or at the work package level or at a lower level if there is significant complexity and risk associated with the task
o. An approach for tracking milestones, costs, risks, subcontractor effort (if applicable), deliverables and proposed internal procedures for assuring timely responses to the Government's needs on any resulting contract.
p. An approach for performance measurement that shall, include establishing an initial plan; defining measurable parameters; defining how these parameters relate to cost and schedule impacts; their approach in providing a detailed schedule that generates a critical path for the project; and a description of the cost-accounting system used or intended to be used based on budget estimates to monitor all costs related to the contract award for both prime- and sub-contractors on a real time bases.

Within fourteen (14) days of the effective date of the BAA award, the Offeror shall submit an updated IPDP which shall be approved by the Project Officer and the Contracting Officer prior to initiation of any activities related to their implementation.

During the course of contract performance, in response to a need to change the IPDP, the Offeror shall submit a Deviation Report. This report shall request a change in the agreed-upon Plan and timelines. This report shall include:

a. Discussion of the justification/rationale for the proposed change.
b. Options for addressing the needed changes from the approved timelines, including a cost-benefit analysis of each option.
c. Recommendations for the preferred option that includes a full analysis and discussion of the effect of the change on the entire product development program, timelines, and budget.

The Offeror shall carry out activities within the contract SOW only as requested and approved by the Contracting Officer, and may not conduct work on the contract without

prior approval from the Contracting Officer, including initiating work that deviates from the agreed-upon IPDP.

2. Target Product Profile (TPP): In their proposal, Offerors shall discuss the TPP of their proposed candidate medical countermeasure. Offerors should use the template in attachment 8 to develop the TPP.

a. The intended use or indication of the proposed medical countermeasure.
b. The intended product profile (strength, quality, purity and identity) noting the performance specifications and features of the medical countermeasure that provide benefit.
c. A description of the medical countermeasure as it is currently configured.
d. A description of the manufacturing process including expected formulation (configuration) of the final product.
e. A description and developmental status of the assays for product release which provide characterization, strength, identity, and purity, as well as any needed assays for product activity and efficacy.
f. Discussions with appropriate FDA reviewers that is relevant to development activities for the proposed medical countermeasure, including plans for generating data to support an Investigational New Drug (IND), Biologics License Application (BLA) or New Drug Application (NDA), Pre-Market Approval and/or 510(k) application: summary of any prior, time-relevant communication with FDA relevant to the product development for the indication noted; summary of audits and inspections relative to the current development or proposed manufacturing (Including at key sub-contractors) of the intended product.

3. Contractor provided Facilities, Infrastructure and other Resources Representative Activities: Depending on the stage of development of the candidate product, this may include but is not limited to:

a. Current facility design including quality control labs for testing & release, laboratory areas supporting formulation and assay development, manufacturing process flow, and animal studies.
b. Major equipment and layout (preliminary piping and instrumentation drawing).
c. Manufacturing capacity expansion plans to match the proposed manufacturing scale up.
d. Overview of the management of Quality Systems at the facility.
e. List of capabilities for clinical activities conducted in house and at contract research organizations.
f. Qualified animal facilities where GLP studies would be conducted and appropriate certifications for humane care and use of vertebrate animals. Detailed instructions on proposal preparation and submission are contained in Part IV.
g. The handling, storing and shipping of potentially dangerous biological and chemical agents, including Select Agents, under biosafety levels required for working with the biological agents under study. Detailed instructions on proposal preparation and submission are contained in Part IV.

h. Validation master plan for key equipment, analytical methods and manufacturing process.

4. Security Plan Representative Activities include but are not limited to:

a. The establishment of a comprehensive security program that provides a security plan for the overall protection of personnel, information, data, and facilities.
b. Security administration, as an element of the security program that address threat and risk assessments and related policies and procedures for personnel security, physical security, information security, information technology.
c. Security management, as an element of the security program that describe each element of security: physical, operations, personnel, information, information technology, transportation; and related training, auditing, and reporting requirements.

Additional information for Security Plan requirements are described in Part IV Section 4, para H and in attachment #4

Part III: Reporting Requirements and Deliverables

Some reports and other deliverables are relevant to specific activities that may or may not be performed during the contract period of performance. The Contractor, the Project Officer and the Contracting Officer shall agree in the final contract negotiations on which reports and other deliverables are relevant and shall be required as deliverables as determined in the negotiated SOW.

As part of the work to be performed under this BAA, the Contractor shall prepare and deliver the following reports throughout the period of performance. For all reports the Contractor shall submit two (2) paper copies and one (1) electronic copy to the Contracting Officer.

Reports:

1. Technical Progress Reports

On the fifteenth (15) day of each month for the previous calendar month, the contractor shall submit to the Project Officer and the Contracting Officer a Technical Progress Report. The frequency of Technical Progress Reporting will be determined by the Contracting Officer and Project Officer during negotiations of the contract. The format and type of Technical Progress Report and Executive Summary will be provided by the Project Officer. The technical Progress Reports will include project timelines and milestones summaries of product manufacturing, testing, and clinical evaluation. A Technical Progress Report will not be required for the period when the Final Report is due. The Contractor shall submit one copy of the Technical Progress Report electronically via e-mail. Any attachments to the e-mail report shall be submitted in Microsoft Word, Microsoft Excel, Microsoft Project, and/or Adobe Acrobat PDF files. Such reports shall include the following specific information:

a. Title page containing: Technical Progress Report, the contract number and title, the period of performance or milestone being reported, the contractor's name, address, and other contact information, the author(s), and the date of submission;
b. Introduction/Background: An introduction covering the purpose and scope of the contract effort;
c. Progress: The report shall detail, document and summarize the results of work performed, test results, milestones achieved during the period covered and cumulative milestones achieved. Also to be included is a summary of work planned for the next two (2) reporting periods on a rolling basis;
d. Issues: Issues resolved, new issues and outstanding issues are enumerated with options and recommendation for resolution. An explanation of any difference between planned progress and actual progress, why the differences have occurred, and, if progress activity is delinquent, then what corrective steps are planned. Revised timelines are provided.
e. Invoices: Summary of any invoices submitted during the reporting period.

f. Action Items: Summary table of activities or tasks to be accomplished by certain date and by whom.
g. Distribution list: A list of persons receiving the Technical Report
h. Attachments: Results on the project are provided as attachments

2. The Executive Summary, which shall accompany each Technical Progress Report, will be formatted in Microsoft Power Point presentations and include the following:

   a. Title page containing Executive Title, the contract number and title, the period of performance or milestone being reported, the contractor's name and the date of submission;
   b. Project Progress presented as milestone events, test results, tasks, and other activities achieved during the reporting period as talking point bullets;
   c. Project issues presented headings and each item as a talking point bullet.

3. Final Report: By the expiration date of the contract, the Contractor shall submit a comprehensive Final Report that shall detail, document, and summarize the results of the entire contract work. The report shall explain comprehensively the results achieved. A draft Final Report will be submitted to the Project and Contracting Officers for review and comments, then the Final Report original, four copies, and an electronic file shall be submitted to the Project and Contracting Officers for distribution to the Program office.

Meetings and Conferences:

The Contractor shall participate in regular meetings to coordinate and oversee the contract effort as directed by the Contracting and Project Officers. Such meetings may include, but are not limited to, meeting of all Contractors and subcontractors to discuss clinical manufacturing progress, product development, product assay development, scale up manufacturing development, clinical sample assays development, pre clinical/clinical study designs and regulatory issues; meetings with individual contractors and other HHS officials to discuss the technical, regulatory, and ethical aspects of the program; and meeting with technical consultants to discuss technical data provided by the Contractor.

Monthly teleconferences between the Contractor and subcontractors and BARDA shall be held to review technical progress. BARDA reserves the right to request more frequent teleconferences and face-to-face meetings depending on the criticality and nature of the work being performed. Contractor will receive feedback from BARDA during the monthly teleconference regarding contract performance. The Contractor will have an opportunity to respond and provide recommendations / remediation plan during the execution of the contract.

Regulatory and Quality Management:

FDA Submissions and meetings:

a. The contractor shall forward the initial draft minutes and final draft minutes of any formal meeting with the FDA to BARDA.

b. The contractor shall forward the final draft minutes of any informal meeting with the FDA to BARDA.
c. The contractor shall forward the dates and times of any meeting with the FDA to BARDA and make arrangements for appropriate BARDA staff to attend FDA meetings.
d. The contractor shall provide BARDA the opportunity to review and comment upon any documents to be submitted to the FDA. The contractor shall provide BARDA with five (5) business days in which to review and provide comments back to the contractor.
e. The contractor shall forward Standard Operating Procedures (upon request from Project Officer/Contracting Officer).
f. The contractor shall provide upon request animal study and/or other technology packages developed under this contract. Packages shall include complete protocols and critical reagents for animal models developed and/or improved with contract funding.
g. The contractor shall provide upon request raw data and/or specific analysis of data generated with USG funds.

Audits / Site Visits:

FDA Audits
Within thirty (30) calendar days of an FDA audit of Contractor or subcontractor facilities, the Contractor shall provide copies of the audit findings, final report, and a plan for addressing areas of nonconformance to FDA regulations and guidance for GLP, GMP or GCP guidelines as identified in the final audit report.

BARDA Audits
The United States Government (USG) reserves the right to conduct an audit of the Contractor with 48 hours notice. The USG reserves the right to accompany the Contractor on routine and for-cause site-visits/audits of subcontractors. At the discretion of the USG and independent of testing conducted by the Contractor, BARDA reserves the right to conduct site visits/audits and collect samples of product held by the Contractor and subcontractors.

Part IV: Proposal Preparation and Submission

Section 1: The Application Process

The application process is in two stages as follows:

Stage 1: Complete a cover sheet, Quad Chart, and White Paper in accordance with the preparation guidance below. Quad Chart and White Paper should describe the effort in sufficient detail to allow evaluation of the concept's technical merit and its potential contribution to the BARDA mission. Offerors whose Quad Chart and White Paper receive a favorable evaluation will be invited to submit a Full Proposal. Offerors whose Quad Chart and White Paper did not receive a favorable evaluation will be notified by email.

Stage 2: Offerors must submit their Full Proposals in accordance with the instructions provided below. Full Proposals will be evaluated against criteria as described in the Evaluation Factors. Proposals that do not conform to the requirements outlined in the BAA or in the invitation will not be reviewed or considered for further action.

Proposal Stage	Deadline for Submission	USG Response
Stage 1: Quad Chart and White Paper	Anytime	Receipt confirmation within 1 week. Decision within 90 days
Stage 2: Full Proposal	Within 90 days of Invitation	Receipt confirmation within 1 week
Source Selection Notification (pending availability of funds)		Within 180 days Full Proposal receipt

Section 2: Stage 1 Quad Chart and White Paper Preparation

Interested offerors shall submit a Quad Chart, and White Paper which expands on the information provided in the Quad Chart. The initial submission is limited (unless otherwise specified in Part VI) to a cover page, one-page Quad Chart, White Paper not to exceed five (5) pages, and an addendum (not to exceed two (2) pages) as discussed below. If submissions exceed these limitations, only those pages previously defined will be reviewed.

Combine all files and forms into a single searchable PDF file before submitting.

Quad Chart Format: All quad charts should include the information indicated on the sample template located in Attachment 7. All Quad Charts should be laid out in landscape format.

1. Heading: Title, Research Area Addressed, Offeror point of contact, Company's Name
2. Upper left: Objective, description of effort

3. Lower left: Benefits of proposed technology, challenges, Specify the maturity of technology research area addressed as indicated by the TRL (Attachment 1&2)
4. Upper right: Picture or graphic
5. Lower Right: Milestones, cost, period of performance.

White Paper Technical Information:

1. A brief technical discussion of the Offeror's objective, approach, and level of effort shall be submitted. Also include the nature and extent of the anticipated results and, if possible, the manner in which the work will contribute to the accomplishment of BARDA's mission and how this would be demonstrated.
2. The cost portion of the White Paper shall contain a brief cost estimate revealing all the component parts of the proposal.
3. As an addendum to the White Paper, include biographical sketches (two pages) of the key personnel who will perform the research, highlighting their qualifications and experience.

Restrictive markings on White Papers: Proposal submissions will be protected from unauthorized disclosure in accordance with FAR Subpart 15.207, applicable law and HHS regulations. Offerors that include in their proposal data that they do not want disclosed shall mark their proposal in accordance with the instructions contained FAR 52.215-1(e) '*Restrictions on disclosure and use of data.'*

Section 3: Quad Chart and White Paper Submission

White Papers must be emailed directly to the following email address: CBRN-BAA@hhs.gov

Include "BAA_BARDA-09-34 QUAD CHART & WHITE PAPER for Research Area #_" in the email subject line. White Papers must be submitted in the following format but do not require any special forms:

• Single PDF formatted file as an email attachment
• Page Size: 8 ½ x 11 inches
• Margins – 1 inch
• Spacing – single
• Font – Arial, 12 point

The file will not exceed 2 Megabytes of storage space. Movie and sound file attachments, URL Links, or other additional files, will not be accepted.

Classification: All Quad Chart and White Paper submissions must be UNCLASSIFIED.

Notification to Offerors: All Offerors will receive a letter and/or an email acknowledging receipt of their Quad Chart and White Paper submission. Offeror's should receive a letter or e-mail within 90 days of submission (Offeror may receive a decision letter sooner than 90 days depending on the number of White Papers submitted to BARDA or if otherwise specified in Part VI: Special Instructions) on the status of whether or not the

Offerors will be invited to submit a Full Proposal. Debriefings for Quad Chart and White Paper will not be provided. However, a brief synopsis of the USG's evaluation in the form of a Summary Statement will be provided upon written request.

IMPORTANT NOTE: Titles given to the White Papers and Full Proposals should be descriptive of the work proposed and not be merely a copy of the title of this solicitation.

Section 4: Stage 2 Full Proposal Preparation

The Full Proposal must be prepared as four separate volumes as follows: Volume I Technical Proposal; Volume I Technical Proposal Appendices; Volume II Cost Proposal; and Volume II Cost Proposal Appendices.

A. Volume I - Technical Proposal

The technical proposal must not exceed 50 pages (unless otherwise specified in Part VI: Special Instructions) including figures, tables and graphs. If the proposal exceeds 50 pages, only the first 50 pages will be reviewed. A page is defined as 8.5 X 11 inches, single-spaced, with one-inch margins in type not smaller than 12 point font.

1. Cover Page: This should include the words "Technical Proposal" and the following:
   - BAA number
   - Title of proposal
   - Identity of prime Offeror and complete list of subcontractors, if applicable
   - Technical contact (name, address, phone/fax, electronic mail address)
   - Administrative/business contact (name, address, phone/fax, electronic mail address)
   - Duration of effort
2. Official Transmittal Letter. This is an official transmittal letter with authorizing official signature.
3. Table of contents: an alphabetical/numerical listing of the sections within the proposal, including corresponding page numbers.
4. Executive Summary
5. Introduction
6. Statement of Work: The SOW should clearly detail the scope and objectives of the effort and the technical approach. It is anticipated that the proposed SOW will be incorporated as an attachment to the resultant award instrument. To that end, the proposal must include a severable, self-standing SOW, without any proprietary restrictions, which can be attached to the contract or agreement award. Include a detailed listing of the technical tasks/subtasks organized by year.

   Development Approach
   a. Non Clinical Research and Development
   b. Process Development, Formulation and Manufacturing Development
   c. Clinical Evaluation

   Management Approach
   d. Integrated Product Development Plan (including Managerial Plan, Quality/Risk Evaluation and Management Strategy, Regulatory

Licensure Plan, Security Plan, Target Product Profile, Facilities, Infrastructure, and Other Resources

7. Project Schedule, Gantt chart and Milestones: A summary of the schedule of events as Work Breakdown Structure (WBS) and milestones.
8. Deliverables: A detailed description of the results and products to be delivered inclusive of the timeframe in which they will be delivered.

B. Volume I – Appendices

Appendices to Volume I contain supplemental data that should accompany the technical proposal. The combined total of Appendices in Volume I should not exceed 50 pages. Additional specific information to be included is referenced below. If a particular item in not relevant to the proposed effort, state that it is not applicable along with any supporting justification.

	Item	Required	Reference
1	Updated Quad Chart	Yes	Template in Attachment #7
2	Protection of Human Subjects	If Applicable	Part IV, Section 4, para F http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm
3	Animal Use	If Applicable	Part IV, Section 4, para G
4	Intellectual Property	Yes	Part IV, Section 4, para I
5	Biographical Sketches	Yes	Part IV, Section 4, para J
6	Use of Select Agents	If Applicable	Part IV, Section 4, para L http://www.cdc.gov/od/sap http://www.aphis.usda.gov/programs/ag_selectagent
7	Laboratory License Requirements	If Applicable	Part IV, Section 4, para N
8	Target Product Profile	Yes	Template in Attachment #8
9	Biographical Sketches	Yes	

C. Volume II – Cost Proposal

The cost proposal shall contain sufficient information for meaningful evaluation, and should not exceed 50 pages (unless otherwise specified in Part VI: Special Instructions). Additionally, a cost summary (not to exceed 2 pages) must be prepared and submitted in conjunction with the detailed cost proposal. The detailed costs must readily track back to the cost presented in the summary and the WBS in the associated Project Gantt Chart. A representative WBS will be available on the medical countermeasures website (www.medicalcountermeasures.gov). The Offeror must also provide a narrative to support the requirements in each cost element. The cost breakdown by tasks

should use the same task numbering as the SOW. Options should be priced separately.

- Basic Cost/Price Information: The business proposal shall contain sufficient information to allow the Government to perform a basic analysis of the proposed cost or price of the work. This information shall include the amounts of the basic elements of the proposed cost or price. These elements will include the following elements by milestone event and/or fiscal or calendar year as applicable:

    i. Direct Labor- Individual labor category or person, with associated labor hours and unburdened direct labor rates;
    ii. Indirect Costs – Fringe Benefits, Overhead, G&A, etc. (Must show base amount and rate);
    iii. Travel – Separate by destinations and include number of trips, durations-number of days, number of travelers, per diem (hotel and meals in accordance with the Federal Travel Regulations,), airfare, car rental, if additional miscellaneous expense is included, list description and estimated amount, etc;
    iv. Subcontract – A cost proposal shall be submitted by the subcontractor. The subcontractor's cost proposal should include on company letterhead the complete company name and mailing address, technical and administrative/business point of contacts, email address, and telephone number. Include the DUNS number.
    v. Consultant – Provide consultant agreement or other document which verifies the proposed loaded daily/hourly rate and labor category;
    vi. Materials should be specifically itemized with costs or estimated costs. Where possible, indicate pricing method (e.g., competition, historical costs, market survey, etc.). Include supporting documentation, i.e. vendor quotes, catalog price lists and past invoices of similar purchases,
    vii. Other Direct Costs, especially any proposed items of equipment. Equipment generally must be furnished by the Offeror. Justifications must be provided when Government funding for such items is sought.
    viii. Fee/profit including percentages.

- Proposal Cover Sheet: The following information shall be provided on the first page of your pricing proposal:

    1. BAA Number;
    2. Title of proposal:
    3. Topical Area:
    4. Name and address of Offeror;
    5. Name and telephone number of point of contact;
    6. Name, address, and telephone number of Contract Administration Office, (if available);
    7. Name, address, and telephone number of Audit Office (if available);
    8. Proposed cost and/or price; profit or fee (as applicable); and total;

9. The following statement: By submitting this proposal, the Offeror, if selected for discussions, grants the Contracting Officer or an authorized representative the right to examine, at any time before award, any of those books, records, documents, or other records directly pertinent to the information requested or submitted.
10. Date of submission; and
11. Name, title and signature of authorized representative.
12. DUNS number and CAGE code.

This cover sheet information is for use by Offerors to submit information to the Government when cost or pricing data are not required but information to help establish price reasonableness or cost realism is necessary. Such information is not considered cost or pricing data, and shall not be certified in accordance with FAR 15.406-2.

A draft template for the breakdown of proposed estimated costs and labor hours is provided in Attachment 3.

D Volume II – Cost Proposal Appendices

Appendices to Volume II contain supplemental data of a cost and non cost nature that should accompany the cost proposal. The combined total of all appendices should not exceed 50 pages. Additional specific information to be included is referenced below. If a particular item in not relevant to the proposed effort, state that it is not applicable along with any supporting justification.

	Item	Required	Reference
1	DUNS, TIN and NAICS	Yes	
2	Certifications and Representations	Yes	Part IV, Section 4, para E
3	CCR	Yes	
4	Security	Yes	Part IV, Section 4, para H Template in Attachment#4
5	Technical Proposal Cost Summary	Yes	Template in Attachment #3
6	HHS Small Business Subcontracting Plan	If Applicable	
7	Summary of Related Activities	Yes	Template in Attachment #5
8	Disclosure of Lobbying Activities	Yes	Part IV, Section 4, para K
9	Report of Government Owned ,	If Applicable	http://www.niaid.nih.gov/contract/forms.htm

	Contractor Held Property		

E. **Representation and Certifications:** In accordance with FAR 4.1201 prospective Offerors shall complete the Online Representations and Certifications Application (ORCA) at http://orca.bpn.gov. Offerors should make mention of its ORCA completion in its proposal and provide it "Certification Validity" period.

F. **Studies That Involve Human Subjects**

All research under this BAA must address the involvement of human subjects and protections from research risk related to their participation in the proposed research plan and comply with 32 CFR 219, 10 U.S.C. 980, and, as applicable, 21 CFR Parts 11, 50, 54, 56, 312)(45 CFR Part 46) and the ICH as well as other applicable federal and state regulations. HHS Policy also requires that women and members of minority groups and their subpopulations: children and the elderly (pediatric and geriatric) must be included in the study population of research involving human subjects, unless a clear and compelling rationale and justification is provided with respect to the health of the subjects or the purpose of the research. The HHS policy on studies that involved human subjects can be accessible through the HHS website: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

G. **Animal Welfare**

If the Offeror proposes to use contract funds to conduct animal studies, the Offeror must demonstrate its understanding and ability to comply with the Public Health Services (PHS) Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/olaw.htm). If the Offeror has an Animal Welfare Assurance on file with the Office of Extramural Research (OER), Office of Laboratory Animal Welfare (OLAW), provide the Assurance number with the proposal. If the Offeror proposes animal studies, the Offeror must submit a plan that describes how the Offeror will comply with the PHS Policy and addresses the five points listed below:

a. Provide a detailed description of the proposed use of the animals in the work outlined in the experimental design and methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
b. Justify the use of animals, the choice of species, and the numbers used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and their numbers.
c. Provide information on the veterinary care of the animals involved.
d. Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices where appropriate to minimize comfort, distress, pain, and injury.
e. Describe any euthanasia method to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association (http://www.avma.org/resources/euthanasia.pdf). If not, present a justification

for not following the recommendations.

H. Security Planning:

The work to be performed under this contract may involve access to sensitive BARDA program information. Therefore, the Offeror(s) shall develop and submit a written Draft Security Plan that describes their procedures and policies to defend against theft, tampering, or destruction of product-related material, equipment, documents, information, and data. Guidance for preparing the security plan can be found in Attachment #4.

The Offeror is invited to submit a request for waiver if he or she believes the proposed work is exempt from some or all of the security requirements listed in Attachment #4 or if the Offeror can demonstrate that commensurate protective measures have been applied that afford an equal level of protection. Requests for waivers should be submitted through the Contracting Officer to the Program Protection Office, BARDA.

I. Intellectual Property:

For issued patents or published patent applications that will be used in the performance of the contract, provide the patent number or patent application publication number, a summary of the patent or invention title, and indicate whether the Offeror is the patent or invention owner.

J. Biographical Sketches:

This Section shall contain the biographical sketches for only the key personnel from both the contractor and subcontractor(s): The Full Proposal must list the names and proposed duties of the professional personnel, consultants, and key subcontractor employees assigned to the project. Their resumes should be included in the appendices in Volume I of the Full Proposal. The resumes should contain information on education, background, recent experience, and specific or technical accomplishments as they pertain to their ability to support the objectives of this project. The approximate percentage of time each individual will be available for this project must be stated. The proposed staff hours of each individual should be allocated against each project task or subtask.

K. Prohibition on the Use of Appropriated Funds for Lobbying Activities HHSAR 352.270-10 Anti-Lobbying (Jan 2006):

The contractor is hereby notified of the restrictions on the use of Department of Health and Human Service's funding for lobbying of Federal, State and Local legislative bodies.

Section 1352 of Title 31, United Stated Code (Public Law 101-121, effective 12/23/89), among other things, prohibits a recipient (and their subcontractors) of a Federal contract, grant, loan, or cooperative agreement from using appropriated funds (other than profits from a federal contract) to pay any person for influencing or attempting to influence an officer or employee of any agency, a Member of Congress, an officer or employee of Congress, or an employee of a Member of Congress in connection with any of the following covered Federal actions; the awarding of any Federal contract; the making of

any Federal grant; the making of any Federal loan; the entering into of any cooperative agreement; or the modification of any Federal contract, grant, loan, or cooperative agreement. For additional information of prohibitions against lobbying activities, see FAR Subpart 3.8 and FAR Clause 52.203-12.

In addition, the current Department of Health and Human Services Appropriations Act provides that no part of any appropriation contained in this Act shall be used, other than for normal and recognized executive-legislative relationships, for publicity or propaganda purposes, for the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television, or video presentation designed to support, or defeat legislation pending before the Congress, or any State or Local legislature except in presentation to the Congress, or any State or Local legislative body itself as stated in P.L. 109-149, Title V, section 503(a), as directed by P.L. 110-5, Div. B, Title I, section 104.

The current Department of Health and Human Services Appropriations Act also provides that no part of any appropriation contained in this Act shall be used to pay the salary or expenses of any contract or grant recipient, or agent acting for such recipient, related to any activity designed to influence legislation or appropriations pending before the Congress, or any State or Local legislature as stated in P.L. 109-149, Title V, section 503(b), as directed by P.L. 110-5, Div. B, Title I, section 104.

L. Use of Select Agent

An HHS chaired committee of contracting, security, safety and scientific program management will assess the applicability of the facilities, regulations, policies, and procedures for meeting the U.S. requirements described in 42 CFR part 73, 7 CFR part 331, and/or 9 CFR part 121.

M. Laboratory License Requirements:

The Contractor shall comply with all applicable requirements of Section 353 of the Public Health Service Act (Clinical Laboratory Improvement Act as amended). This requirement shall also be included in any subcontract for services under the contract.

N. Advanced Understandings

1. Invoices: Cost and Personnel Reporting, and Variances from the Negotiated Budget:

    i. The contractor agrees to provide a detailed breakdown on invoices of the following cost categories:

        a. Direct Labor - List individuals by name, title/position, hourly/annual rate, level of effort, and amount claimed.
        b. Fringe Benefits - Cite rate and amount
        c. Overhead - Cite rate and amount
        d. Materials & Supplies - Include detailed breakdown when total amount is over $1,000.
        e. Travel - Identify travelers, dates, destination, purpose of trip, and amount. Cite COA, if appropriate. List separately, domestic travel, general scientific meeting travel, and foreign travel.
        f. Consultant Fees - Identify individuals and amounts.

g. Subcontracts - Attach subcontractor invoice(s).
h. Equipment - Cite authorization and amount.
i. G&A - Cite rate and amount.
j. Total Cost
k. Fixed Fee
l. Total CPFF

Monthly invoices must include the cumulative total expenses to date, adjusted (as applicable) to show any amounts suspended by the Government.

ii. The contractor agrees to immediately notify the Contracting Officer in writing if there is an anticipated overrun (any amount) or unexpended balance (greater than 10 percent) of the amount allotted to the contract, and the reasons for the variance. Also refer to the requirements of the Limitation of Cost (FAR 52.232-20) clause in the contract.

2. Publications: Any manuscript or scientific meeting abstract containing data generated under this contract must be submitted for BARDA Project Officer review no less than thirty (30) calendar days for manuscripts and fifteen (15) calendar days for abstracts before submission for public presentation or publication. Contract support shall be acknowledged in all such publications. A "publication" is defined as an issue of printed material offered for distribution or any communication or oral presentation of information.

3. Press Releases: The Contractor agrees to accurately and factually represent the work conducted under this contract in all press releases. Misrepresenting contract results or releasing information that is injurious to the integrity of BARDA may be construed as improper conduct. Press releases shall be considered to include the public release of information to any medium, excluding peer-reviewed scientific publications. The contractor shall ensure that the Project Officer has received an advance copy of any press release related to this contract not less than four (4) working days prior to the issuance of the press release.

4. Human Subjects: Research projects involving humans and/or human specimens can only be initiated with written approval by the BARDA Project Officer.

The Good Clinical Practice Regulations (GCP)(21 CFR Parts 50, 54, 56 312)(45 CFR Part 46)(ICH E6) as well as other applicable federal and state regulations will be standards that apply for use of human subject and/or human specimens in clinical studies.

If at any time during the life of the contract, the Contractor fails to comply with GCP as identified by regulations outline above , the Offeror shall have thirty (30) calendar days from the time such material failure is identified to cure such or initiate cure to the satisfaction of the USG Project Officer. If the Offeror fails to take such an action within the thirty (30) calendar day period, then the contract may be terminated.

5. Monthly Conference Calls: A conference call between the USG Project Officer and the Offerors shall occur monthly, or as directed by the Project Officer. During this call the Principal Investigator will discuss the activities during the reporting period, any problems

that have arisen and the activities planned for the ensuing reporting period. The first reporting period consists of the first full month of performance plus any fractional part of the initial month. Thereafter, the reporting period shall consist of each calendar month. Offerors may choose to include other key personnel on the conference call to give detailed updates on specific projects or this may be requested by the Project Officer.

6. Export control notification: Offerors are responsible for ensuring compliance with all export control laws and regulations that maybe applicable to the export of and foreign access to their proposed technologies. Offerors may consult with the Department of State with any questions regarding the International Traffic in Arms Regulation (ITAR) (22 CRF Parts 120-130) and /or the Department of Commerce regarding the Export Administration Regulations (15 CRF Parts 730-774).

7. Manufacturing Standards:

The Good Manufacturing Practice Regulations (GMP)(21 CFR Parts 210-211) and regulations pertaining to biological products (21 CFR Part 600) and regulations pertaining to diagnostic products (21 CFR Part 860) will be the standard to be applied for manufacturing, processing, packaging, storage and delivery of this product.

If at any time during the life of the contract, the Contractor fails to comply with GMP in the manufacturing, processing, packaging, storage, stability and other testing of the manufactured drug substance or product and delivery of this product and such failure results in a material adverse effect on the safety, purity or potency of the product (a material failure) as identified by the FDA , the Offeror shall have thirty (30) calendar days from the time such material failure is identified to cure such material failure. If the Offeror fails to take such an action to the satisfaction of the USG Project Officer within the thirty (30) calendar day period, then the contract may be terminated.

8. Prohibition on contractor Involvement with Terrorist Activities: The Contractor acknowledges that U.S. Executive Orders and Laws, including but not limited to Executive Order 13224 and Public Law 107-56, prohibit transactions with, and the provision of resources and support to, individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all subcontracts issued under this contract.

9. Subcontracting Plans: Successful contract proposals that exceed $550,000, submitted by all but small business concerns, will be required to submit a Small Business Subcontracting Plan in accordance with FAR 52.219-9.

10. Identification and Disposition of Data: the Contractor will be required to provide certain data generated under this contract to the HHS. HHS reserves the right to review any other data determined by HHS to be relevant to this contract. The contractor shall keep copies of all data required by the FDA relevant to this contract for the time specified by the FDA.

11. Confidentiality of Information: The following information is covered by HHSAR Clause 352.224-70, confidentiality of Information (January 2006): Data obtained from human subjects.

Section 5: Full Proposal Submission

Mail an original and five (5) copies of the Full Proposal and two (2) electronic copies (CD or DVD) to the following address:

Contracting Officer
Biomedical Advanced Research and Development Authority
330 Independence Ave, S.W.
Room G640
Washington, D.C. 20201

Offeror shall include in the Full Proposal Cover Sheet:

- The name, title, mailing address, telephone number, and fax number of the company or organization;
- The name, title, mailing address, telephone number, fax number, and e-mail address of the division point of contact regarding decisions made with respect to the Offeror and who can obligate the proposal contractually;
- The name, title, mailing address, telephone number, fax number, and e-mail address and those individual(s) authorized to negotiate with the USG; and
- A statement indicating you are submitting a final Full Proposal for consideration.

Submission file format for the electronic copy: Each volume of the proposal must be submitted as a separate and searchable Portable Document File (PDF) compatible with Adobe Acrobat version 7.0 or earlier. Each individual file shall not exceed 10 megabytes of storage space.

Notification to Offerors: All Offerors will receive an email acknowledging receipt of their Quad Chart/White Paper and Full Proposal.

Withdrawal of Proposals:

1. Proposal may be withdrawn by written notice received at any time before award. Withdrawals are effective upon receipt of notice by the Contracting Officer via email.

2. The government may reject Full Proposal submissions that are deemed non-compliant, i.e., that significantly deviate from the instructions in the Broad Agency Announcement or invitation to submit a full proposal

Information to be requested from Successful Offerors: Offerors whose proposals are selected for potential award will be contacted to provide additional administrative information if required for award. Such information may include explanations and other information applicable to the proposed award.

Offerors that are not responsive in a timely manner to Government requests for information (defined as meeting Government deadlines established and communicated with the request) may be removed from award consideration. Offerors that request significant revisions to their proposal subsequent to their selection for potential award may be removed from award consideration. Offerors may also be removed from award consideration if the Offeror and the Government fail to negotiate mutually agreeable terms within a reasonable period of time.

All proposals are treated as privileged information prior to award and the contents are disclosed only for the purpose of evaluation. The Offeror must indicate any limitation to be placed on disclosure of information contained in the proposal in accordance with the instructions contained FAR 52.215-1(e) '*Restrictions on disclosure and use of data.'*

Section 6: General Information

PRELIMINARY INQUIRIES: BARDA realizes that the preparation of a research proposal often represents a substantial investment of time and effort by the Offeror. Therefore, in an attempt to minimize this burden, BARDA encourages organizations and individuals interested in submitting research proposals to make preliminary inquiries as to the general need for the type of research effort contemplated, before expending extensive effort in preparing a detailed research proposal or submitting proprietary information. The POCs for each area of interest are identified in Part I of this announcement.

CLASSIFIED SUBMISSIONS: Classified proposals will not be accepted.

USE OF COLOR IN PROPOSALS: All proposals received shall be stored as electronic images. Electronic color images require a significantly larger amount of storage space than black-and-white images. As a result, Offerors' use of color in proposals should be minimal and used only when absolutely necessary for details. Do not use color if it is not necessary.

POST EMPLOYMENT CONFLICT OF INTEREST: There are certain post employment restrictions on former federal officers and employees, including special government employees (Section 207 of Title 18, U.S.C.). If a prospective Offeror believes a conflict of interest may exist, the situation should be emailed to this address CBRN-BAA @hhs.gov, prior to expending time and effort in preparing a proposal. The appropriate BARDA personnel will discuss with any conflict of interest with prospective Offeror.

UNSUCCESSFUL PROPOSAL DISPOSITION: Unless noted in an Offeror's proposal to the contrary, unsuccessful full proposals will be retained for six (6) months from declination and then properly destroyed.

Part V: Proposal Evaluation

A. Evaluation Criteria:

The selection of one or more sources for award will be based on an evaluation of each Offeror's Quad Chart and White Paper and Full Proposal. The Quad Chart and White Paper and Full Proposal will be evaluated by a peer or scientific review process and will be evaluated based on the following criteria that are listed in descending order of importance pursuant to FAR 35.016. The sub-criteria listed under a particular criterion are of equal importance to each other.

a. Program relevance

1. Medical countermeasures that align with the projected near or mid-term objectives identified in the *PHEMCE Implementation Plan for CBRN Threats*.
2. Medical countermeasures that focus on diagnosis, post-event prophylaxis, post-exposure treatment/mitigation, and are also effective when administered within the treatment window for that agent.
3. Medical countermeasures that are readily administered during a public health emergency. For instance, oral, self administration is preferred over intra-muscular (i.m.) or subcutaneous (s.c.) injection, and i.m. or s.c. injection is preferred over intravenous administration from a logistical and emergency response perspective. Medical countermeasures whose developmental maturity aligns with TRLs 6 to 7 or Diagnostic TRLs 5 to 6 (Attachment 1 and 2).

b. The overall scientific and technical merits of the proposal

1. The degree of innovation and potential to offer a revolutionary increase in capability or a significant reduction in cost commensurate with the potential risks of the innovative approach.
2. The soundness, feasibility, and validity of the proposed plans, methods, techniques, and procedures of the technical proposal.
3. The Offeror's understanding of the scope and the technical effort needed to address it.
4. The reasonableness of the proposed schedule.
5. The Offeror's understanding of the statutory and regulatory requirements for FDA licensure.
6. Ownership of Intellectual Property.

c. The Offeror's capabilities, related experience, and past performance, including the qualifications, capabilities, and experiences of the proposed key personnel

1. The quality of technical personnel proposed.
2. The Offeror's experience in relevant efforts with similar resources.
3. The ability to manage the proposed effort.

d. Cost realism and reasonableness. Each price / cost response will be reviewed for price / cost realism, reasonableness, and overall best value to the government. Members of the review team may presume that the technical approach provided by the Offeror serves as a rationale for the labor mix and labor hours used.

e. For contract awards to be made to large businesses, the socio-economic merits of each proposal will be evaluated, but not scored, based on the extent of the Offeror's commitment in providing meaningful subcontracting opportunities for small businesses, small disadvantaged businesses, woman-owned businesses, service disabled veteran-owned small businesses, Hub-zone small business concerns, historically black colleges and universities, and minority institutions.

f. For contracts, preference for Offerors providing U.S. based jobs in the technical and /or administrative activities needed to accomplish milestone activities associated with product development will be afforded if the assessment on other criteria is equal.

The final evaluation will be based on an assessment of the overall best value to the government based on these criteria. Awards, if any, will be made based on proposal evaluation, funds availability, and other programmatic considerations. Award is also dependent upon demonstration by the applicant that they have adequately addressed the following requirements:

a. Research involving Human Subjects/Anatomical Substances (if proposed).
b. Research involving Animals (if proposed).
c. Evidence of GLP Compliance (if appropriate).
d. Evidence of GMP Compliance (if appropriate).
e. Evidence of GCP Compliance (if appropriate).
f. Evidence of Laboratory Licensure Requirements (if appropriate)
g. Use of Select Agents (if appropriate)
h. All required Representations and Certifications are completed and on file.

The Quad Chart and White Paper and Full Proposal will be evaluated and categorized as follows:

CAT I Well conceived, scientifically, and technically sound proposals important to program goals and objectives. Proposals in Category I are recommended for acceptance subject to funds availability.

CAT II Scientifically and technically sound proposals important to program goals and objectives that may require further development and may be recommended for acceptance subject to funds availability. CAT II proposals are at a lower priority than CAT I

CAT III Proposals not technically sound or do not meet program goals and objectives. CAT III proposals have the lowest priority and will be rejected.

Offerors selected for negotiations may be subject to inspections of their facilities and Quality Assurance/Quality Control (QA/QC) capabilities. The decision to inspect specific

facilities will be made by the Project Officer in coordination with the Contracting Officer. If inspections are performed during the negotiations, the results of the inspection will be considered in final selection for award of a contract. Offerors, including proposed subcontractors, will be requested to make all non-proprietary records, including previous regulatory inspection records, and staff available in response to a pre-award site visit or audit by BARDA or its designee. Pre-award site visits may be made with short notice. Offerors are expected to guarantee the availability of key staff or other staff determined by the Government as essential for purposes of this site visit.

B. Past Performance Information

Past performance information will be evaluated to the extent of determining the Offerors ability to perform the contract successfully. Offerors shall submit the following information as part of their proposal.

The Offeror shall provide a list of the last three (3) government contracts during the past three years and all contracts currently being performed that are similar in nature to the BAA workscope. Contracts listed may include those entered into by the Federal Government, agencies of state and local governments and commercial concerns. Offerors may also submit past performance information regarding predecessor companies, key personnel who have relevant experience or subcontractors that will perform major or critical aspects of the requirement when such information is relevant to the instant acquisition. For the purposes of this BAA, a "major subcontract" is defined as a subcontract that exceeds $25,000.

Include the following information for each contract or subcontract listed:

1. Name of Contracting Organization
2. Contract Number (for subcontracts, provide the prime contract number and the subcontract number)
3. Contract Type
4. Total Contract Value
5. Description of Requirement
6. Contracting Officer's Name and Telephone Number
7. Program Manager's Name and Telephone Number
8. North American Industry Classification System Code

The Offeror may provide information on problems encountered on the identified contracts and the Offeror's corrective actions.

The Government is not required to contact all references provided by the Offeror. Also, references other than those identified by the Offeror may be contacted by the Government to obtain additional information that will be used in the evaluation of the Offeror's past performance.

Part VI: Special Instructions

A. The following are special instructions for Offerors submitting Quad Chart and White Paper for area of interest # 1: Vaccines (Anthrax vaccines will have priority consideration in fiscal year 2009).

Quad Chart and White Paper will be accepted no later than close of business on March 24, 2009 for consideration in fiscal year 2009 contract award.

B. The following are special instructions for Offerors submitting Quad Chart and White Paper for area of interest # 2: Antitoxins and Therapeutics.

Offerors that are developing anthrax antitoxins that are based on monoclonal antibodies are invited to submit White Papers outlining plans for the advanced development of those candidate products. Offerors must have completed a Phase 1 clinical trial. The proposal shall include clinical and nonclinical studies through Phase 2 trials and the assay or process development needed to support those studies. The proposal may include manufacturing scale-up but shall not include consistency runs or pivotal studies that are dependent on that material.

Quad Chart and White Paper will be accepted no later than close of business on March 24, 2009 for consideration in fiscal year 2009 contract award.

C. The following are special instructions for Offerors submitting Quad Chart and White Paper for area of interest # 4: Radiological/Nuclear Agent Medical Countermeasures.

The page limit is increased for Part IV: Proposal Preparation and Submissions, Section 2: Stage 1 Quad Chart and White Paper Preparation as follows: initial submission is limited to a one page Quad Chart, a cover page, a White Paper not to exceed ten (10) pages and an addendum (not to exceed three (3) pages) as discussed below.

The page limit is increased for Part IV: Proposal Preparation and Submissions, Section 4: Stage 2 Full Proposal Preparation as follows:

Volume I – Technical Proposal shall not exceed 100 pages
Volume 2 – Cost Proposal shall not exceed 100 pages

D. The following are special instructions for Offerors submitting Quad Chart and White Paper for area of interest # 5: Chemical Agent Medical Countermeasures:

The page limit is increased for Part IV: Proposal Preparation and Submissions, Section 2: Stage 1 Quad Chart and White Paper Preparation as follows: initial submission is limited to a one page Quad Chart, a cover page, a White Paper not to exceed ten (10) pages and an addendum (not to exceed three (3) pages) as discussed below.

The page limit is increased for Part IV: Proposal Preparation and Submissions, Section 4: Stage 2 Full Proposal Preparation as follows:

Volume I – Technical Proposal shall not exceed 100 pages
Volume 2 – Cost Proposal shall not exceed 100 pages

Part VII: Attachments

Attachment 1: (Draft) Technology Readiness Level (TRL) Definitions for Drugs and Biologics

TRLs provide a systematic metric/measurement system that supports assessments of the maturity of a particular technology and the consistent comparison of maturity between different types of technology. TRLs were originally developed and used by the National Aeronautics and Space Administration (NASA) for technology planning. The use of TRLs has been widely adopted in government and industry. ***The work under this BAA will be TRL 6 to 7.***

Level	Integrated Medical Countermeasure Technology Readiness Level
3	Target/Candidate identification and Characterization of Preliminary Candidate(s) Begin research, data collection, and analysis in order to test hypothesis. Explore alternative concepts, identify and evaluate critical technologies and components, and begin characterization of candidate(s). Preliminary efficacy demonstrated *in vivo*.
4	**Candidate Optimization and Non-GLP *In Vivo* Demonstration of Activity and Efficacy** Integration of critical technologies for candidate development. Initiation of animal model development. Non-GLP *in vivo* toxicity and efficacy demonstration in accordance with the product's intended use. Initiation of experiments to identify markers correlates of protection, assays, and endpoints for further non-clinical and clinical studies. *Animal Models:* Initiate development of appropriate and relevant animal model(s) for the desired indications. *Assays:* Initiate development of appropriate and relevant assays and associated reagents for the desired indications. *Manufacturing:* Manufacture laboratory-scale (i.e. non-GMP) quantities of bulk product and proposed formulated product. **4A** Demonstrate non-GLP *in vivo* activity and potential for efficacy consistent with the product's intended use (i.e. dose, schedule, duration, route of administration, and route of threat agent challenge). **4B** Conduct initial non-GLP toxicity studies and determine pharmacodynamics and pharmacokinetics and/or immune response in appropriate animal models (as applicable). **4C** Initiate experiments to determine assays, parameters, surrogate markers, correlates of protection, and endpoints to be used during non-clinical and clinical studies to further evaluate and characterize candidate(s).

5	**Advanced Characterization of Candidate and Initiation of GMP Process Development** Continue non-GLP *in vivo* studies and animal model and assay development. Establish draft Target Product Profiles. Develop a scalable and reproducible manufacturing process amenable to GMP. *Animal Models:* Continue development of animal models for efficacy and dose-ranging studies. *Assays:* Initiate development of in-process assays and analytical methods for product characterization and release, including assessments of potency, purity, identity, strength, sterility, and quality as appropriate. *Manufacturing:* Initiate process development for small-scale manufacturing amenable to GMP. *Target Product Profile:* Draft preliminary Target Product Profile. Questions of shelf life, storage conditions, and packaging should be considered to ensure that anticipated use of the product is consistent with the intended use for which approval will be sought from FDA. **5A** Demonstrate acceptable Absorption, Distribution, Metabolism and Elimination characteristics and/or immune responses in non-GLP animal studies as necessary for IND filing. **5B** Continue establishing correlates of protection and/or surrogate markers for efficacy for use in future GLP studies in animal models. Identify minimally effective dose to facilitate determination of "humanized" dose once clinical data are obtained.
6	**GMP Pilot Lot Production, IND Submission, and Phase 1 Clinical Trial(s)** Manufacture GMP pilot lots. Prepare and submit Investigational New Drug (IND) package to FDA and conduct Phase 1 clinical trial(s) to determine the safety and pharmacokinetics of the clinical test article. *Animal Models:* Continue animal model development via toxicology, pharmacology, and immunogenicity studies. *Assays:* Qualify assays for manufacturing quality control and immunogenicity, if applicable. *Manufacturing:* Manufacture, release and conduct stability testing of GMP bulk and formulated product in support of the IND and clinical trial(s). *Target Product Profile:* Update Target Product Profile as appropriate. **6A** Conduct GLP animal studies for toxicology, pharmacology, and immunogenicity as appropriate. **6B** Prepare and submit full IND package to FDA to support initial clinical trial(s). **6C** Complete Phase 1 clinical trial(s) that establish an initial safety and pharmacokinetics assessment.

7	Scale-up, Initiation of GMP Process Validation, and Phase 2 Clinical Trial(s)3 Scale-up and initiate validation of GMP manufacturing process. Conduct animal efficacy studies as appropriate[4]. Conduct Phase 2 clinical trial(s)[3]. Animal Models: Refine animal model development in preparation for pivotal GLP animal efficacy studies. Assays: Validate assays for manufacturing quality control and immunogenicity if applicable. Manufacturing: Scale-up and validate GMP manufacturing process at a scale compatible with GOVERNMENT requirements. Begin stability studies of the GMP product in a formulation, dosage form, and container consistent with Target Product Profile. Initiate manufacturing process validation and consistency lot production. Target Product Profile: Update Target Product Profile as appropriate. 7A Conduct GLP animal efficacy studies as appropriate for the product at this stage1.[4] 7B Complete expanded clinical safety trials as appropriate for the product (e.g., Phase 2)[3].

3 Identification of later regulatory stages of clinical development in this document (e.g., Phase 2, Phase 3) may not apply to some products being developed under the 'Animal Rule'. Other than human safety and pharmacology studies, no additional clinical data may be feasible or ethical to obtain.

4 These could include GLP animal efficacy studies required by FDA at this stage in support of an Emergency Use Authorization (EUA). Requirements for issuance of an EUA will be handled on a case-by-case basis and will depend on the nature and extent of the threat at any point during the product development timeline, from the initiation of Phase 1 studies through licensure or approval. GLP animal efficacy study requirements may also vary by product type (e.g., vaccine, therapeutic, prophylactic) and U.S. government agency program office.

Attachment 2: (Draft) Technology Readiness Level (TRL) Definitions for Medical In-Vitro Diagnostic Devices

Notice: This document does not serve as official FDA Guidance nor does it represent the Agency's current thinking on this topic. For the purposes of a regulatory application seeking licensure/approval, additional data may be required by FDA. ***The work under this BAA for Medical In-Vitro Diagnostic Devices will be TRL 5-6.***

TRL 1 Basic Research

Generation of scientific knowledge of fundamental phenomena. Findings are peer reviewed and serve as foundation for new technologies.

Decision Criteria: Literature reviews, market surveys, White Papers.

TRL 2 Basic Invention

Intense focus on experimental designs for possible application of scientific approach to a specific problem.

Decision Criteria: Hypothesis-based research and development efforts. Research plans and protocols are developed, peer-reviewed, and approved for funding. Design controls instituted.

TRL 3 Initial Validation of Analytical Components

Basic hypothesis-based research, data collection analysis to test hypothesis and explore alternatives. Initial test of design concepts. Critical components defined and tested independently (the term component is defined in 820.3(c)). Product design and development plan drafted.

Decision Criteria: Initial proof of concept for device demonstrated in a limited number of laboratory experiments; may use surrogate or spiked samples.

TRL 4 Transition from Research to Development

Non-GLP research to define parametric data required for assessment. Initial specifications for device, systems, and subsystems determined. Device evaluation at in-house laboratories. Procedures and methods to be used during non-clinical, pre-clinical, and clinical studies in evaluating devices and systems are identified. Potential safety problems identified through risk analysis. Ad hoc hardware in a laboratory. Basic software as applicable.

Decision Criteria: Proof of concept demonstrated for devices with laboratory procedures defined. Feasibility data collected to identify a diagnostic target or signal that will be of value in diagnosis of biothreat agents.

AT THIS POINT (IF NOT SOONER), THE FDA SHOULD BE CONTACTED FOR PRE- IDE MEETINGS TO DISCUSS PRDUCT INTENDED USE, ANALYTICAL/CLIICAL STUDY DESIGNS AND REGULATORY STRATEGY RE: NEED FOR AN IDE, PRE-MARKET APPLICATION (PMA OR 510K), AND PRODUCT DEVELOPMENT PROTOCOLS (PDP)

TRL 5 Product Development/ Begin Design Controls

Assessment of existing diagnostic modalities and how the new device relates to these other approaches. Intended use and indications for use defined. Tissue, organ, or body fluid spiked samples are evaluated. Suppliers and service providers qualified and type and extent of control defined. Purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use defined and balanced. Components integrated and tested as systems and subsystems.

Decision Criteria: Devices tested through simulations. Pre-IDE submitted to and reviewed by

FDA–CDRH to determine if analytical and clinical evaluations proposed are appropriate for intended use.

TRL 6 Pre-Clinical / In-House Testing

Demonstrate analytical and functional characteristics of the device in a controlled laboratory setting, and initiate testing on appropriate clinical samples. Initiate validation master plan for critical processes and prepare final assembly of components. Manufacturing personnel participate in the design process up front to facilitate transfer of design to manufacturing.

Candidate Diagnostic Device: Analytical performance assessed (including analytical sensitivity, in-house precision, and analytical specificity) by testing real or simulated samples of interest.

IDE Ready: A full package, including the clinical evaluation protocol, is prepared for submission to the FDA (if a significant risk device study), for submission to an IRB (if a non-significant risk device study), or for submission to an IRB (if waived according to FDA exemptions from IDE requirements 812.2(c)(3)).

Decision Criteria: Evidence supports proceeding to pre-clinical studies.

TRL 7 Investigational Phase

Functional and pre-clinical testing begun with fully integrated device (systems and subsystems). Manufacturing process is validated and initial production units used for final design verification and validation activities. Continued interactions with FDA-CDRH.

Decision Criteria: Pre-clinical and functional testing completed. Design verification completed for the final product. Initial commercial scale devices are produced; release criteria established. Preliminary data collected and presented and discussed with CDRH. IDE submitted and approved by FDA-CDRH as applicable (21 CFR Part 812).

TRL 8 End of System Development; Use in Actual Setting with Clinical Samples

Clinical evaluations implemented for assessing diagnostic accuracy of device for its intended use. Risk/benefit for use of device is assessed. Data in support of product labeling for directions-for-use is established; any needed lot consistency/reproducibility studies completed. Design locked final review and approval prior to final transfer to manufacturing. Pre-Market Approval (PMA) and/or 510(k) application to FDA-CDRH submitted.

Decision Criteria: Approval of the PMA or as applicable clearance of the 510(k) by FDA-CDRH.

TRL 9 Used in Clinical Settings with Clinical Samples, Post-Market Studies or Data Collec

When appropriate, post-marketing surveillance data collection studies to monitor device performance under broader conditions for use.

Decision Criteria: None - continued surveillance. Corrective and Preventive Action Program to monitor performance.

Attachment 3: Volume II - Breakdown Of Proposed Estimated Cost (Plus Fee) And Labor Hours

INSTRUCTIONS FOR USE OF THE FORMAT

1. This format has been prepared as a guideline. It may require amending to meet the specific requirements of this BAA. For example, this BAA may require the submission of cost/price data for three years listed on this form. If this BAA is phased, identify each phase in addition to each year. Total each year, phase, and sub-element.

2. This format shall be used to submit the breakdown of all proposed estimated cost elements. List each cost element and sub-element for direct costs, indirect costs and fee, if applicable. In addition, provide detailed calculations for all items. For example:

    a. For all personnel, list the skill / labor category, rate per hour and number of hours proposed. If a pool of personnel is proposed, list the composition of the pool and how the cost proposed was calculated. List the factor used for prorating Year One and the escalation rate applied between years.

        Offeror's proposal should be stated in the same terms as will be used to account for and record the effort under a contract. If percentages of effort are used, the basis to which such percentages are applied must also be submitted by the Offeror. The attached format should be revised to accommodate direct labor proposed as a percentage of effort.

    b. For all materials, supplies, and other direct costs, list all unit prices, etc., to detail how the calculations were made.
    c. For all indirect costs, list the rates applied and the base the rate is applied to.
    d. For all travel, list the specifics for each trip.
    e. For any subcontract proposed, submit a separate breakdown format.
    f. Justification for the need of some cost elements may be listed as an attachment, i.e., special equipment, above average consultant fees, etc.

3. If the Government has provided "uniform pricing assumptions" for this BAA, the Offeror must comply with and identify each item.

4. It is requested that you use the spreadsheet that is provided below to prepare your business proposal. For security purposes, please include a hard copy of the completed spreadsheet and submit the electronic file on a diskette with your proposal.

BREAKDOWN OF PROPOSED ESTIMATED COST (PLUS FEE) AND LABOR HOURS

COST ELEMENT	Year 1	Year 2	Year 3	
Labor Category	(Rate / Hours)	(Rate / Hours)	(Rate / Hours)	Total
DIRECT LABOR COST:	$	$	$	$
MATERIAL COST:	$	$	$	$
TRAVEL COST:	$	$	$	$
OTHER (Specify)	$	$	$	$
OTHER (Specify)	$	$	$	$
TOTAL DIRECT COST:	$	$	$	$
FRINGE BENEFIT COST: (if applicable) % of Direct Labor Cost	$	$	$	$
INDIRECT COST: % of Total Direct Cost	$	$	$	$
TOTAL COST:	$	$	$	$
FIXED FEE: (if applicable) % of Total Est. Cost	$	$	$	$
GRAND TOTAL ESTIMATED CPFF)	$	$	$	$

Attachment 4: Security Template

Section I. <u>Security Administration:</u>

1. Security Program: The Offeror shall have a comprehensive security program that provides a security plan for the overall protection of personnel, information, data, and facilities associated with fulfilling the BARDA requirement. The Offeror's proposal shall include a security plan which establishes security practices and procedures that demonstrate how the Offeror will meet and adhere to the security requirements outlined in Section II (noted below) by time of contract award. The Offeror shall also ensure that other entities (sub-contractors, consultants, etc.) performing work on behalf of the Offeror establishes and manages a security program that is in compliance with BARDA security requirements.

2. Facility Security Plan: The Offeror's security plan will include the following processes and procedures at a minimum:

(a) Security Administration: Organization and responsibilities; security risk assessment for site; threat levels identification; security procedures during elevated threats; liaison with law enforcement; security education and training.

(b) Personnel Security Policies and Procedures*:* Candidate recruitment process; background investigations; employment suitability policy; access determination; rules of behavior/ conduct; termination procedures; non-disclosure agreements.

(c) Physical Security Policies and Procedures: Internal / external access control; protective services; identification/ badging; visitor access controls; parking areas and access control; perimeter fencing / barriers; shipping, receiving and transport; security lighting; restricted areas; signage; intrusion detection systems; alarm monitoring / response; closed circuit television; product storage security; other control measures.

(d) Information Security: Identification of sensitive information; access control; storage of information; document control; retention/ destruction requirements.

(e) Information Technology Security Policies and Procedures: Intrusion detection and prevention systems; employee training; encryption systems; identification of sensitive information/ media; password policy; removable media policy; laptop policy; media access control/ determination; secure storage; system document control; system backup; system disaster recovery.

3. Site master plan: Offeror shall provide a site schematic for security systems which includes: main access points; security cameras; electronic access points; bio-containment laboratories.

4. Site threat / risk assessment: Offeror shall provide a written risk assessment for the facility addressing: criminal threat; terrorist threat; industrial espionage; natural disasters; and potential loss of critical infrastructure (power/water/natural gas, etc.) This assessment shall include recent data obtained from local law enforcement agencies.

Section II. <u>Security Requirements:</u>

1. Physical Security:

(a) **Closed Circuit Television (CCTV) Monitoring:**

- CCTV with time lapse video recording for exits / entrances to the facility and buildings where critical assets are processed and stored.
- Video recordings maintained for a minimum of 30 days.

(b) **Lighting**:

- Lighting covering perimeter, parking areas, entrances/exits. Lighting should have emergency power backup and be sufficient for CCTV.

(c) **Receiving and Shipping:**

- Receiving and shipping areas must have controlled access and contingency plans that implement modified procedures to restrict shipping and receiving to mission critical products during times of elevated threat.

(d) **Physical Access Control:**

- Intrusion Detection System with centralized monitoring system capability.
- Immediate notification / response to any alarms.
- Electronic system (i.e. card key) utilized to control access to areas where assets critical to the contract are located (facilities, laboratories, clean rooms, production facilities, warehouses, etc.)

(e) **Employee/Visitor Identification:**

- Photo identification for all personnel displayed at all times.
- Visitor control; identification; screening and accountability system.

(f) **Security Fencing:**

- Requirements for security fencing will be determined by the criticality of the program and the potential threat environment.

(g) **Protective Security Forces:**

- Requirements for a security force at the facility will be determined by the criticality of the program and the potential threat environment.

2. Security Operations:

(a) **Information Sharing:**

- Establish liaison with law enforcement and procedures for receiving and disseminating threat information.

(b) **Training:**

- Conduct new employee security awareness training.
- Conduct and maintain records of annual security awareness training.

(b) **Security Management:**

- Designate a knowledgeable employee to manage security operations.

3. Personnel Security:

(a) **Records Checks / Interview:**

- Verification of date of birth; citizenship; education; previous employment (5 year history); previous residences (5 year history); national / local criminal records search; and a personal interview of candidate.

(b) **Hiring / Retention Standards:**

- Policies concerning hiring and retention of employees to include employee conduct and behavior standards.

4. Information Security:

(a) **Physical Document Control:**

- Applicable documents shall be identified and marked as procurement sensitive, proprietary or with appropriate government markings.
- Sensitive, proprietary and government documents should be maintained in a lockable filing cabinet / desk or other storage device.

(b) **Document Destruction**

- Documents shall be destroyed using approved destruction measures (i.e. shredders / third party vendor / pulverizing / incinerator).

5. Information Technology Security:

(a) **Access:**

- Limit information system access to authorized users.
- Identify information system users, processes acting on behalf of users, or devices and authenticate identities before allowing access.
- Limit physical access to information systems and equipment.

(b) **Training:**

- Ensure that personnel are trained and are made aware of the security risks associated with their activities and of the applicable laws, policies, standards, regulations, or procedures related to IT systems.

(c) **Audit and Accountability:**

- Create, protect, and retain information system audit records to the extent needed to enable the monitoring, analysis, investigation, and reporting of unlawful, unauthorized, or inappropriate information system activity; and ensure that the actions of individual information system users can be uniquely traced to those users.

(d) **Configuration Management:**

- Establish and enforce security configuration settings.

(e) **Contingency Planning:**

- Establish, maintain, and implement plans for emergency response, backup operations, and post-disaster recovery for information systems to ensure the availability of critical information resources.

(f) **Incident Response:**

- Establish an operational incident handling capability for information systems that includes adequate preparation, detection, analysis, containment, and recovery.

(g) **Media Protection:**

- Protect information system media, both paper and digital; limit access to information on information system media to authorized users; and sanitize or destroy information system media no longer needed.

(h) **Physical / Environmental Protection:**

- Limit physical access to information systems, equipment, and the respective operating environments to authorized individuals; protect the physical and support infrastructure for information systems;
- Protect information systems against environmental hazards; provide appropriate environmental controls in facilities containing information systems.

6. Transportation Security: Adequate security controls shall be implemented to protect materials while in transit from theft, destruction, manipulation, or damage. These security measures will be addressed in the Facility Security Plan.

7. Security Reporting Requirements: The Offeror shall immediately report to the government any activity or incident that is in violation of established security standards or indicates the loss or theft of government products. The facts and circumstances associated with these incidents will be documented in writing for government review.

8. Security Audits: The Offeror agrees to formal security audits conducted at the discretion of the government. Security audits may include both prime and sub locations.

Attachment 5: Summary of Related Activities

The following specific information must be provided by the Offeror pertaining to the Project Director, Principal Investigator, and each of any other proposed key professional individuals designated for performance under any resulting contract.

a. Identify the total amount of all presently active federal contracts/cooperative agreements/grants and commercial agreements citing the committed levels of effort for those projects for each of the key individuals***** in this proposal.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

*****If an individual has no obligation(s), so state.

b. Provide the total number of outstanding proposals, exclusive of the instant proposal, having been submitted by your organization, not presently accepted but in an anticipatory stage, which will commit levels of effort by the proposed professional individuals*****.

Professional's Name and Title/Position:

Identifying Number	Agency	Total Effort Committed
1.		
2.		
3.		
4.		

*****If no commitment of effort is intended, so state.

c. Provide a statement of the level of effort to be dedicated to any resultant contract awarded to your organization for those individuals designated and cited in this proposal.

Name	Title/Position	Total Proposed Effort
1.		
2.		

Attachment 6: Government Notice for Handling Proposals

NOTE: This Notice is for the Technical Evaluation Review Panel who will be reviewing the proposals submitted in response to this BAA. THE OFFEROR SHALL PLACE A COPY OF THIS NOTICE BEHIND THE TITLE PAGE OF EACH COPY OF THE TECHNICAL PROPOSAL.

This proposal shall be used and disclosed for evaluation purposes only, and a copy of this Government notice shall be applied to any reproduction or abstract thereof. Any authorized restrictive notices which the submitter places on this proposal shall be strictly complied with. Disclosure of this proposal outside the Government for evaluation purposes shall be made only to the extent authorized by, and in accordance with, the procedures in HHSAR 352.215-1.

(f) If authorized in agency implementing regulations, agencies may release proposals outside the Government for evaluation, consistent with the following:

(1) Decisions to release proposals outside the Government for evaluation purposes shall be made by the agency head or designee;

(2) Written agreement must be obtained from the evaluator that the information (data) contained in the proposal will be used only for evaluation purposes and will not be further disclosed;

(3) Any authorized restrictive legends placed on the proposal by the prospective Contractor or subcontractor or by the Government shall be applied to any reproduction or abstracted information made by the evaluator;

(4) Upon completing the evaluation, all copies of the proposal, as well as any abstracts thereof, shall be returned to the Government office which initially furnished them for evaluation; and

(5) All determinations to release the proposal outside the Government take into consideration requirements for avoiding organizational conflicts of interest and the competitive relationship, if any, between the prospective Contractor or subcontractor and the prospective outside evaluator.

(g) The submitter of any proposal shall be provided notice adequate to afford an opportunity to take appropriate action before release of any information (data) contained therein pursuant to a request under the Freedom of Information Act (5 U.S.C. 552); and, time permitting, the submitter should be consulted to obtain assistance in determining the eligibility of the information (data) in question as an exemption under the Act. (See also Subpart 24.2, Freedom of Information Act.)

Attachment 7: Quad Chart and White Paper Format Template

I. Quad Chart Template

A quad chart that contains the following information must be included in Volume III, Supplemental Information, of the Phase II Full Proposal and must be positioned in a landscape view. Any quad chart submitted that exceeds the one-page limit will not be read or evaluated. Please note that the Title of the Project should be different than that of the Topic.

TITLE OF PROJECT, RESEARCH AREA ADDRESSED, PROGRAM DIRECTOR/MANAGER, COMPANY NAME

Objective: Clear, concise (2-3 sentences) description of the objectives and methodologies of the effort. Description of effort: A bullet list (2-3) of the primary scientific challenges being addressed	Picture or Graphic that Illustrates the research or concept
Benefits of Proposed Technology: Challenges: Maturity of Technology:	Bullet list of the major goals/milestones by Project Year Proposed Funding Year 1 Dates Year 2 Dates Year 3 Dates Contact Information (name, email, phone)

II. White Paper Template

The White Paper narrative expands on the Quad Chart presentation.
White Paper Technical Content:

1. A brief technical discussion of the effort's objective, approach, and level of effort shall be submitted. Also include the nature and extent of the anticipated results and, if known, the manner in which the work will contribute to the accomplishment of BARDA's mission and how this would be demonstrated.
2. The cost portion of the White Paper shall contain a brief cost estimate revealing all the component parts of the proposal.
3. As an addendum to the White Paper, include biographical sketches (two pages) of the key personnel who will perform the research, highlighting their qualifications and experience.

Attachment 8: Target Product Profile Template

REGULATORY GUIDANCE FOR DRUGS AND BIOLOGICS (MAY BE MODIFIED FOR USE WITH DEVICES)

Target Product Profile Template

Target Product Profile: *Drug Name*

Milestone (meeting or submission)	Date	*TPP Submitted? Y/N	TPP Version Date	TPP Discussed? Y/N
Pre-IND				
IND Submission				
EOP1				
EOP2A				
EOP2/Pre-Phase 3				
Pre-NDA/BLA				
Other (specify)				

* The TPP can be submitted to the FDA as part of a Briefing Document or as a stand-alone document.

1 Indications and Usage

Target	**Annotations**
A statement that the drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, OR *A statement that the drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, OR* *A statement that the drug is indicated for the relief of symptoms associated with a disease or syndrome, OR* *A statement that the drug is indicated for a particular indication only in conjunction with a primary mode of therapy*	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *When listing studies, consider:* *The intent to develop evidence to support safety and efficacy in selected subgroups (i.e., limitations of use)* *Tests needed for selection or monitoring of patients (i.e., susceptibility tests)* *Whether safety considerations require the drug to be reserved for certain situations (i.e., in refractory patients)* *Whether the drug is to be used on a chronic basis* *What evidence will be developed to support comparator statements regarding safety or effectiveness*

Comments:

2 Dosage and Administration

Target	**Annotations**
For each indication, state the following:	*Summary information regarding completed or*

Route of administration *Recommended usual dose* *Dose range shown to be safe and effective* *Exposure (dose- or blood level-response relationship, if any)* *Dosage intervals or titration schedule* *Usual duration of treatment course when treatment is not chronic* *Dosage adjustments (e.g., in specific genotypes, pediatric patients, geriatric patients, or patients with renal or hepatic disease)* *Tests for guiding dosing (e.g., target plasma drug levels, therapeutic range, response biomarkers)*	*planned studies to support the safety and effectiveness of the proposed dosage and route of administration:* *Protocol #, Serial #, Submission date*

Comments:

3 Dosage Forms and Strengths

Target	**Annotations**
Include information on the available dosage forms, including strength or potency of dosage form in metric system and a description of identifying characteristics of dosage forms	*Summary information regarding completed or planned studies to support the dosage forms and strengths:* *Protocol #, Serial #, Submission date*

Comments:

4 Contraindications

Target	**Annotations**
List situations in which the drug might be contraindicated, including: *Increased risk of harm because of age, sex, concomitant therapy, disease state* *Adverse reactions which would limit use* *Known, not theoretical, hazards*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date* *Or, literature references describing contraindication for drug class.*
Comments:	

5 Warnings and Precautions

Target	**Annotations**
Include a description of clinically significant adverse reactions and potential safety hazards and limitations of use because of safety considerations, as reasonable evidence of these issues is established or suspected during the drug development program. A causal relationship need not be demonstrated. *Include information regarding any special care to be exercised for safe use, including precautions that are not required under any other section of the label.* *Identify any laboratory tests helpful in following*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date* *Or, literature references describing significant adverse reactions shared by the drug class of the new drug.*

the patient's response or in identifying possible adverse reactions.	
Comments:	

6 Adverse Reactions

Target	**Annotations**
Describe overall adverse reaction profile of the drug based on entire safety database. List adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable. Within a listing, adverse reactions should be categorized by body system, severity of the reaction, or in order of decreasing frequency, or by a combination of these, as appropriate. Within a category, adverse reactions should be listed in decreasing order of frequency. Include the studies in the development program that will address adverse reactions associated with a particular drug class.	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*
Comments:	

7 Drug Interactions

Target	**Annotations**
Describe clinically significant interactions, either observed or predicted (i.e., other prescription drugs or over-the-counter drugs, class of drugs, or foods such as grapefruit juice or dietary supplements); practical advice on how to prevent drug-drug interactions; (description of results from studies conducted or observations from the integrated safety summary); drug-laboratory test interactions (known interference of drug with lab test outcome).	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

8 Use in Specific Populations

Target	**Annotations**
Consider the following: Limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the population.	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date If there are no plans to study the drug in a specific population, include rationale.*

Comments:

8.1 Pregnancy *(This subsection can be omitted if the drug is not absorbed systemically)**:***

Teratogenic effects: Pregnancy Categories: A, B, C, D, X
Nonteratogenic effects: Other effects on reproduction, the fetus, or newborn.
8.2 Labor and Delivery: *Use during labor or delivery, effects on mother, fetus, duration of labor, delivery, and effects on later growth of newborn.*
8.3 Nursing Mothers: *If the drug is absorbed systemically, information about excretion of drug in human milk and effects on the nursing infant. Describe pertinent adverse events in animal offspring or tumorigenicity potential if it is detected or suspected.*
8.4 Pediatric Use: *Statements relevant to the use of the drug product in the pediatric population (birth to 16 years of age). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the pediatric population.*
8.5 Geriatric Use: *Statements relevant to the use of the drug product in the geriatric population (age 65 and older). Cite any limitations, need for monitoring, specific hazards, differences in response, or other information pertinent to the referenced population.*
8.6 Additional Subsections: *Use of drug in other specified populations (e.g., those with renal or hepatic impairment).*

9 Drug Abuse and Dependence

Target	**Annotations**
Include the following subsections, as appropriate for the drug:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

9.1 Controlled Substance:*Anticipated DEA schedule.*
9.2 Abuse:*Identify types of abuse and adverse reactions pertinent to them. Identify particularly susceptible patient populations.*
9.3 Dependence*:Discuss potential for dependence and describe the characteristic effects resulting from psychological or physical dependence.*

10 Overdosage

Target	**Annotations**
Provide specific information about: *Signs, symptoms, and lab findings associated with an overdosage of the drug* *Complications that can occur with overdose of the drug (e.g., organ toxicity)* *Concentrations of the drug in biofluids associated with toxicity or death* *The amount of the drug in a single overdose that is ordinarily associated with symptoms, and the amount of the drug in a single overdose that is likely to be life-threatening* *Whether the drug is dialyzable* *Recommended general treatment procedures*	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *Update with human data, if available.*

Comments:

11 Description

Target	**Annotations**

Include the proprietary name and established name, dosage form and route of administration, qualitative and quantitative ingredients, pharmacologic or therapeutic class, and any other important physical and chemical characteristics.	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

12 Clinical Pharmacology

Target	**Annotations**
Include a concise factual summary of the clinical pharmacology and actions of the drug in humans. Data that describe the drug's pharmacologic activity can be included in this section, including biochemical or physiological mechanism of action, pharmacokinetic information, degree of absorption, pathway for biotransformation, percent dose unchanged, metabolites, rate of half-lives including elimination concentration in body fluids at therapeutic and toxic levels, degree of binding to plasma, degree of uptake by a particular organ or fetus, and passage across the blood-brain barrier. Include the following subsections:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date* *If applicable, a subsection (e.g., 12.4 Microbiology) can be created under this section heading and all of the microbiology information for antimicrobial products consolidated into that subsection.*

Comments:

12.1 Mechanism of Action:*Summarize* ***established*** *mechanisms of action in humans at various levels (e.g., receptor membrane, tissue, organ, whole body). Do not include theorized mechanisms of action.*

12.2 Pharmacodynamics:*Include a description of any biochemical or physiologic pharmacologic effects of the drug or active metabolites related to the drug's clinical effect or those related to adverse effects or toxicity. Include data on exposure-response relationship and time course of pharmacodynamic response.*

12.3 Pharmacokinetics:*Describe clinically significant pharmacokinetics of a drug or active metabolites (i.e., pertinent absorption, distribution, metabolism, and excretion parameters). Include results of pharmacokinetic studies that establish the absence of an effect, including pertinent human studies and in vitro data.*

13 Nonclinical Toxicology

Target	**Annotations**
Include the following subsections, as appropriate:	*Summary information regarding completed or planned studies to support the target: Protocol #, Serial #, Submission date*

Comments:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility:

Results of long-term carcinogenicity studies — species identified

Mutagenesis results
Reproduction study results
13.2 Animal Toxicology and/or Pharmacology: *Ordinarily, significant animal data necessary for safe and effective use of the drug in humans should be included in other sections of the labeling, as appropriate. If the pertinent animal data cannot be appropriately incorporated into other sections of the labeling, this subsection can be used.*

14 Clinical Studies

Target	**Annotations**
Provide a description of studies that support statements about the efficacy or safety benefits. Consider including a description of supporting tables and graphs.	*Summary information about completed or planned studies regarding the intent to develop evidence to support benefits of treatment (i.e., safety or efficacy benefits of primary or secondary endpoints in the selected population):* *Protocol #, Serial #, Submission date* *Measurement instruments (e.g., patient-reported outcomes instrument) and references to supporting development and validation documentation* *Also consider including where the studies will be (or have been) run (i.e., geographical area).*
Comments:	

15 References — *Can include when labeling must summarize or otherwise rely on recommendation by authoritative scientific body, or a standardized methodology, scale, or technique, because information is necessary for safe and effective use.*

16 How Supplied/Storage and Handling

Target	**Annotations**
Include information about the available dosage forms to which the labeling will apply and for which the manufacturer or distributor will be responsible. For example: *Strength of the dosage form* *Units in which the dosage form ordinarily is available* *Information to facilitate identification of dosage forms* *Special handling and storage conditions*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date*
Comments:	

17 Patient Counseling Information

Target	**Annotations**
Include information for prescribers to convey to patients to use the drug safely and effectively. For example: *Precautions concerning driving*	*Summary information regarding completed or planned studies to support the target:* *Protocol #, Serial #, Submission date*

Concomitant use of other substances that may have harmful additive effects *Proper use and disposal of syringes and needles* *Adverse reactions reasonably associated with use of the drug* *Lab tests and monitoring required* *Indicate whether a Patient Package Insert or MedGuide are planned.*	
Comments:	

1. This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.
2. For the purposes of this guidance, all references to *drug* include both human drugs and therapeutic biological products unless otherwise noted.
3. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page athttp://www.fda.gov/cder/guidance/index.htm.
4. See the guidance for industry *Fast Track Drug Development Programs — Designation, Development, and Application Review*(http://www.fda.gov/cder/guidance/index.htm).
5. A clean copy of the Target Product Profile Template can be found at http://www.fda.gov/cder/regulatory/TPP/default.htm.
6. http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

ATTACHMENT 9 - REGULATORY GUIDANCE FOR DEVICES

Overview of Device Regulations (cf. http://www.fda.gov/cdrh/devadvice/overview.html)
Introduction
FDA`s Center for Devices and Radiological Health (CDRH) is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. In addition, CDRH regulates radiation-emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.
Radiation-emitting Electronic Products
Medical devices are classified into Class I, II, and III. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval. A description of device classification and a link to the Product Classification Database is available at "Classification of Medical Devices."
The basic regulatory requirements that manufacturers of medical devices distributed in the U.S. must comply with are:
Establishment registration,
Medical Device Listing,
Premarket Notification 510(k), unless exempt, or Premarket Approval (PMA),
Investigational Device Exemption (IDE) for clinical studies
Quality System (QS) regulation,
Labeling requirements, and
Medical Device Reporting (MDR)

Establishment Registration - 21 CFR Part 807
Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. All establishment registrations must be submitted electronically unless a waiver has been granted by FDA. All registration information must be verified annually between October 1st and December 31st of each year. In addition to registration, foreign manufacturers must also designate a U.S. Agent. Beginning October 1, 2007, most establishments are required to pay an establishment registration fee.
Establishment Registration
U.S. Agents

Medical Device Listing - 21CFR Part 807
Manufacturers must list their devices with the FDA. Establishments required to list their devices include:
manufacturers,
contract manufacturers that commecially distribute the device,
contract sterilizers that commercially distribute the device,
repackagers and relabelers,
specification developers,
reprocessors single-use devices,
remanufacturer
manufacturers of accessories and components sold directly to the end user
U.S. manufacturers of "export only" devices
Medical Device Listing

Premarket Notification 510(k) - 21 CFR Part 807 Subpart E
If your device requires the submission of a Premarket Notification 510(k), you cannot commercially distribute the device until you receive a letter of substantial equivalence from FDA authorizing you to do so. A 510(k) must demonstrate that the device is substantially equivalent to one legally in commercial distribution in the United States: (1) before May 28, 1976; or (2) to a device that has been determined by FDA to be substantially equivalent.
Premarket Notification 510(k)
On October 26, 2002 the Medical Device User Fee and Modernization Act of 2002 became law. It authorizes FDA to charge a fee for medical device Premarket Notification 510(k) reviews. A small business may pay a reduced fee. The application fee applies to Traditional, Abbreviated, and Special 510(k)s. The payment of a premarket review fee is not related in any way to FDA's final decision on a submission.
510(k) Review Fees
Most Class I devices and some Class II devices are exempt from the Premarket Notification 510(k) submission. A list of exempt devices is located at:
510(k) Exempt Devices
If you plan to send a 510(k) application to FDA for a Class I or Class II device, you may find 510(k) review by an Accredited Persons beneficial. FDA accredited 12 organizations to conduct a primary review of 670 types of devices. By law, FDA must issue a final determination within 30 days after receiving a recommendation from an Accredited Person. Please note that 510(k) review by an Accredited Person is exempt from any FDA fee; however, the third-party may charge a fee for its review.
Third Party Review

Premarket Approval (PMA) - 21 CFR Part 814
Product requiring PMAs are Class III devices are high risk devices that pose a significant risk of illness or injury, or devices found not substantially equivalent to Class I and II predicate through the 510(k) process. The PMA process is more involved and includes the submission of clinical data to support claims made for the device.
Premarket Approval
Beginning fiscal year 2003 (October 1, 2002 through September 30, 2003), medical device user fees apply to original PMAs and certain types of PMA supplements. Small businesses are eligible for reduced or waived fees.
PMA Review Fees

Investigational Device Exemption (IDE) - 21CFR Part 812
An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification 510(k) submission to FDA. Clinical studies with devices of significant risk must be approved by FDA and by an Institutional Review Board (IRB) before the study can begin. Studies with devices of nonsignificant risk must be approved by the IRB only before the study can begin.
Investigational Device Exemption

Quality System Regulation (QS)/Good Manufacturing Practices (GMP) - 21 CFR Part 820
The quality system regulation includes requirements related to the methods used in and the facilities and controls used for: designing, purchasing, manufacturing, packaging, labeling, storing, installing and servicing of medical devices. Manufacturing facilities undergo FDA inspections to assure compliance with the QS requirements.
Quality System
The quality system regulation includes design controls (21 CFR 820.30) which must comply with during the design and development of the device. Information on design controls can be found in the following guidance documents:
Design Control Guidance for Medical Device Manufacturers
Do It By Design - An Introduction to Human Factors in Medical Devices
Medical Device Quality Systems Manual: A Small Entity Compliance Guide

Labeling - 21 CFR Part 801
Labeling includes labels on the device as well as descriptive and informational literature that accompanies the device.
Labeling

Medical Device Reporting - 21 CFR Part 803
Incidents in which a device may have caused or contributed to a death or serious injury must to be reported to FDA under the Medical Device Reporting program. In addition, certain malfunctions must also be reported. The MDR regulation is a mechanism for FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The goals of the regulation are to detect and correct problems in a timely manner.
Medical Device Reporting